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BULLETIN

OF THE

JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

Vol. XLVIII, No. 5 MAY, 1931

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PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS

BALTIMORE, MARYLAND

Made in United States of America

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

BULLETIN
OF
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This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

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THE JOHNS HOPKINS PRESS
BALTIMORE, MARYLAND, U. S. A.

FOETAL BLOOD STUDIES

II. The Lactic Acid Content of Umbilical Cord Blood under Various Conditions[1]

N. J. EASTMAN and C. M. McLANE

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Since lactic acid is the characteristic product of anäerobic metabolism in the animal body, its accumulation in the tissues and the blood constitutes our most reliable indication of oxygen deficiency. Thus, during vigorous exercise, as the oxygen supplied by the blood becomes insufficient to oxidize the lactic acid formed by the muscular contractions, this acid mounts rapidly in the blood to reach concentrations of over 100 mg. per 100 cc., a value about five times the normal one (1, 2). Similarly, if the oxygen supply to the brain is experimentally diminished by occlusion of the cerebral vessels or by the injection of sodium cyanide, there occurs an excessive production of lactic acid in the cells of that organ (3). It is believed, indeed, that the detrimental effects of anoxemia are in large part due to the cellular changes dependent upon the accumualtion of such acid products of metabolism (4).

To the foetus *in utero*, particularly during labor, the problem of oxygen want would seem to be a rather pressing one. In the first place, its arterial blood, reaching it through the umbilical vein, is low in oxygen as judged by adult standards; indeed, it was estimated in the first paper (5) of this series that the oxygen unsaturation of foetal blood as it exists in the capillaries is more than three times that of the corresponding maternal blood and consequently that the full-term foetus *in utero* must exist normally in a state of considerable cyanosis. These deductions were based entirely on the nature of our oxygen findings in the blood of the umbilical vessels and did not take into consideration the anatomical "shunts" of the foetal circulation. These latter, it may be noted, will diminish still further the oxygen content of the blood actually available for foetal metabolism. Since at birth the placental circulation is impaired by the retracting uterus,

[1] Submitted for publication February 1, 1931.

the oxygen supply to the foetus at that time will become even more reduced, and depending on the type of the delivery, may reach a very low level.

While the problem of oxygen want, then, would appear to be an imminent one for the foetus, the study of this question by means of lactic-acid determinations on foetal blood has apparently never been attempted. Blair Bell (6), however, in connection with certain studies on glucolysis in malignant neoplasms, made determinations of the lactic acid content of the umbilical blood following normal delivery and found it to be extraordinarily high, ranging over 60 mg. per 100 cc. on an average, as compared with only 38 mg. per 100 cc. in the blood of the maternal arm vein. He reported, moreover, that the blood of the umbilical artery contained much more lactic acid than that of the umbilical vein and concluded that there was normally a considerable production of this acid in the foetal organism at term. Boǫkelmann (7), in a careful investigation of the lactic acid content of maternal blood at various stages of gestation, found that it averaged 44.9 mg. per 100 cc. during the second stage of labor and rose slightly higher immediately after delivery. The latter author did not extend his studies to include the blood of the umbilical cord.

It is the purpose of the present communication to report a study of the lactic acid content of maternal and umbilical blood in 24 cases. Since our interest has centered chiefly on the possibile relationship between blood lactic acid in the foetus and the onset of respiration, we have included in our series seven cases of definite foetal asphyxia. These were all sufficiently severe to require resuscitative procedures for periods varying from five to twenty minutes. The three babies, who died, were alive at birth as evidenced by the heart beat, as well as by occasional feeble attempts at respiration, and at autopsy none of them showed cerebral hemorrhage or other obvious cause of death. The blood specimens were obtained immediately after delivery by the same procedures as described in our previous paper (5). The lactic acid determinations were done by the method of Friedemann and Kendall (8), care being taken to prepare the blood filtrates immediately after securing the blood. All estimations were carried out in duplicate, the technique being checked at frequent intervals by analyses of standard solutions of zinc lactate. Since parallel determinations on

the same blood never varied more than 3 mg. per 100 cc., we believe that differences in our figures in excess of that amount are probably significant.

RESULTS

The detailed results of the study are listed in Table I, while our average values for blood lactic acid in the various conditions investigated are shown diagrammatically in Chart I. It appears evident

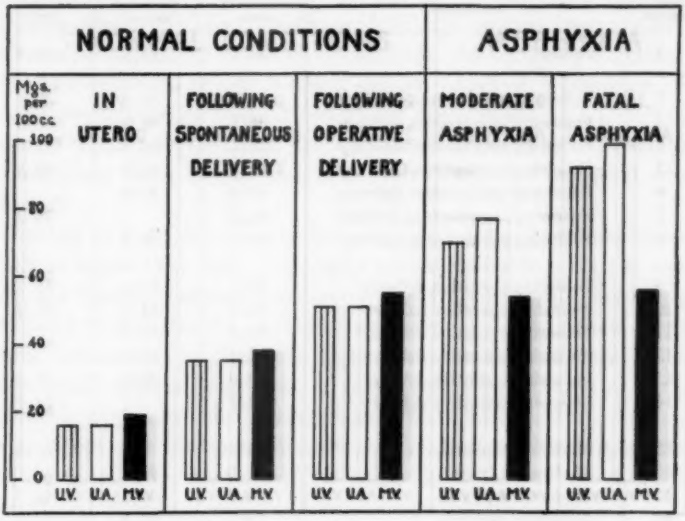

CHART 1. SHOWING THE AVERAGE LACTIC ACID CONTENT OF THE UMBILICAL VEIN BLOOD (*U.V.*), THE UMBILICAL ARTERY BLOOD (*U.A.*), AND THE MATERNAL VEIN BLOOD (*M.V.*), UNDER VARIOUS CONDITIONS

from our figures that the blood lactic acid of the foetus as it exists *in utero* is well within normal limits. Furthermore, the fact that the arterial and venous bloods of the foetus *in utero* show no detectable differences in lactic acid content indicates that normally little of this acid is produced in the foetal tissues. Similarly, at the moment of birth, the lactic acid content of the umbilical vein blood and that of the umbilical artery blood, although at higher levels than *in utero*, appear to be identical.

The high lactic acid content of the umbilical cord blood following spontaneous delivery was a constant finding in our series, the figures ranging from 28 to 45 mg. per 100 cc., with an average of 35. Under

TABLE 1

Showing the lactic acid content of the umbilical vein, the umbilical artery, and the maternal vein bloods under various conditions

The figures represent mg. of lactic acid per 100 cc. of blood.

CASE NUMBER	CONDITION	UMBILICAL VEIN	UMBILICAL ARTERY	MATERNAL VEIN
1	*In utero*	16.7	16.6	19.4
2	Following spontaneous delivery	35.1	34.1	37.9
3	Following spontaneous delivery	36.5	38.0	38.3
4	Following spontaneous delivery	28.1	28.4	31.7
5	Following spontaneous delivery	44.8	45.6	49.3
6	Following spontaneous delivery	40.0	39.8	
7	Following spontaneous delivery	31.3		34.2
8	Following spontaneous delivery	34.2	34.2	
9	Following operative delivery	53.2	53.6	55.2
10	Following operative delivery	55.0	54.9	57.4
11	Following operative delivery	50.7	51.3	
12	Following operative delivery	39.0	38.6	
13	Following operative delivery	50.0	50.0	53.3
14	Following operative delivery	52.7		54.7
15	Moderate asphyxia	66.3		49.0
16	Moderate asphyxia	81.0	90.5	
17	Moderate asphyxia	58.9	66.2	56.7
18	Moderate asphyxia	73.0	77.3	
19	Moderate asphyxia	69.4	76.4	56.4
20	Moderate asphyxia	71.8	79.1	53.7
21	Moderate asphyxia	70.1		55.5
22	Fatal asphyxia	90.3	101.0	
23	Fatal asphyxia	95.7		57.0
24	Fatal asphyxia	89.2	97.3	

normal conditions, however, this elevated blood lactic acid present at birth does not seem to be of foetal origin, but appears to represent rather the result of a diffusion of this acid from the mother, whose blood lactic acid at the moment of delivery has been increased by the

muscular exercise incident to labor. Such an interpretation of the phenomenon is warranted not only by the fact that the lactic acid contents of the umbilical vein and artery bloods are consistently the same, but also by the close relationship existing between the concentration of this acid in the maternal blood, on the one hand, and in the umbilical blood, on the other. This relationship holds good, it will be noted, at levels ranging from 16 to 45 mg. per 100 cc., the maternal blood averaging 2 to 4 mg. per 100 cc. higher. Similarly, in operative deliveries when the blood lactic acid of the mother becomes still further elevated as the result of anaesthesia, the lactic acid contents of the two umbilical bloods follow it closely. Indeed, it has been our experience that under normal conditions there exists at all levels a constant relationship between the lactic acid contents of the blood of the umbilical vein, of the umbilical artery, and the maternal vein (Chart I).

Turning now to our results in cases of definite foetal asphyxia, it will be noted that this relationship no longer holds. On the contrary, the blood of the umbilical artery shows a substantial increase in lactic acid over that of the umbilical vein, while in both of these foetal bloods the amount is distinctly higher than in the maternal blood, which would appear to indicate a very definite production of lactic acid in foetal tissues. In passing, it may be mentioned that the oxygen contents of these foetal bloods also showed marked departures from the normal, the amount of this gas in the umbilical vein blood of asphyxiated infants being reduced to concentrations as low as 2 volumes per cent, while that in the umbilical artery blood was diminished to a fraction of 1 volume per cent. Indeed, in one of our fatal cases of asphyxia, no oxygen was demonstrable either in the blood of the umbilical vein or in that of the umbilical artery. Finally, it was found that in an approximate way the accumulation of lactic acid in the foetus parallels the degree of this anoxemia, levels above 90 mg. per 100 cc. being associated with foetal death.

COMMENT

On the basis of the evidence here presented it appears that the blood lactic acid of the foetus at birth originates in one of two ways; and in respect to foetal metabolism it may be either exogenous or endog-

enous. In the former instance, it is derived by simple diffusion from the blood of the mother, the ultimate source of the lactic acid being maternal tissue; in the latter, it appears to originate in the asphyxiated foetal tissues themselves, whence it passes by osmosis into the foetal blood stream. Chiefly as a result of the influence of the buffer mechanism of the blood, the lactic acid arising in the two locations will produce, we believe, two quite different effects on the foetal organism, —effects which have seemed to us of particular interest in connection with the onset of respiration in the new-born.

It will be recalled that lactic acid never exists as such in the blood stream, but is present only in the form of a neutral salt, presumably sodium lactate. This fact, of course, is the result of the action of the strong blood buffers, the lactic acid ion displacing the HCO_3 ion from the blood sodium bicarbonate with the result that the released carbon dioxide is eliminated through the lungs and the pH of the blood maintained practically constant. Whenever we speak, therefore, of lactic acid diffusing freely through the placenta, we refer in reality to the ready diffusibility of the neutral salt of lactic acid. It will be noted further in this connection that before maternal lactic acid can reach the tissues of the foetus, it must encounter not only the buffers of the maternal blood but those of the foetal blood as well. While our imperfect knowledge of placental interchange precludes sweeping conclusions from these facts, the evidence nevertheless suggests that the lactic acid which diffuses from the mother to the foetus can have little effect upon the hydrogen-ion concentration either of foetal blood or foetal tissues as long as the maternal blood buffers retain their potency. Since the blood lactic acid of the mother is regularly elevated at delivery, the increased lactic acid found in the normal foetus at birth is usually exogenous in origin and, for the reasons stated, apparently exerts but little influence on foetal functions.

The effects of endogenous lactic acid formation in the foetus are more difficult to evaluate. On the one hand, it seems clear that, as long as the placental circulation is intact, normal foetal tissues do not produce detectable amounts of this substance and that the foetal organism *in utero*, although supplied by blood which is relatively low in oxygen, does not normally suffer oxygen want. It seems equally evident, on the other hand, that a foetus which is subjected to ex-

treme anoxemia, as exemplified by our cases of asphyxia, produces substantial quantities of lactic acid in its tissues. From these facts it seems probable that the normal infant at birth, as it becomes subjected to the gradual increasing oxygen deprivation associated with uterine contractions, must likewise form lactic acid. But whether the lactic acid thus formed becomes physiologically active, and whether it influences respiration and other phenomena at birth, are questions that cannot be answered on a sound basis in the present state of our knowledge. Judging from the high concentrations of blood lactic acid exhibited by asphyxiated infants, it may be suspected that such babies are in a state of considerable acidosis. Again, however, the precise degree of acidosis existing will be determined by the efficiency of the blood and tissue buffers and it has therefore seemed more fitting to discuss this aspect of foetal asphyxia in a future communication in which the hydrogen-ion concentration of the blood of normal and asphyxiated infants will be reported.

CONCLUSIONS

1. The blood lactic acid of the foetus *in utero* is within normal limits.

2. The blood lactic acid of infants *at birth* is regularly elevated, the figures in the present series ranging from 28 to 45 mg. per 100 cc., with an average of 35.

3. In normal infants this increased blood lactic acid content at birth is due to simple diffusion from the mother, whose blood lactic acid at the moment of delivery is increased as the result of the muscular activity incident to labor.

4. In asphyxiated infants a very definite endogenous production of lactic acid occurs, the blood lactic acid levels rising above those in the maternal blood to reach concentrations as high as 90 mg. per 100 cc.

5. The high concentration of blood lactic acid exhibited by asphyxiated infants makes it seem probable that asphyxia neonatorum is associated with considerable acidosis; but in the present state of our knowledge we hesitate to draw conclusions as to how important a factor it may be.

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THE STRUCTURE OF THE RENAL TUBULE OF THE TOADFISH[1]

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Since the toadfish (Opsanus tau) is in many ways extremely suitable for the functional study of the aglomerular kidney, and since a considerable number of physiological observations have been made on the toadfish in this laboratory, a study of the nature of the epithelium of its renal tubule has been undertaken. When the aglomerular nature of this kidney was first reported by Marshall (1929), he stated that careful study of sections indicated that the renal epithelium, exclusive of the collecting tubule, was high cuboidal and rodded throughout. Moreover, special fixation and staining at that time showed the presence of brush border in the great majority of the tubules examined. Nevertheless, the possibility remained that some portion of the tubule might not possess brush border. To settle this question conclusively seemed of such great importance from the standpoint of the final interpretation of physiological observations that a thorough study of several serially sectioned tubules was undertaken.

For this purpose, complete serial sections were prepared at 5μ from material fixed in Bensley's A. O. B. fluid (glacial acetic acid, 1 drop; osmic acid, 4 cc. of a 1 per cent solution; potassium bichromate, 8 cc. of a 2.5 per cent solution) and stained with iron hematoxylin. Two renal tubules were followed from their blind endings to their union with a larger collecting tubule. The topography of these tubules was determined accurately by making camera lucida drawings of each section. Subsequently one of the tubules was reconstructed by the Born wax plate method (Figs. 1 and 2).

Investigation of the present material has demonstrated conclusively that in the toadfish the cells of the renal tubule, to the point of junction

[1] Submitted for publication February 20, 1931.

with the collecting tubule, are invariably provided with brush border. It is therefore definitely proved that there is no segment devoid of brush border. Figure 3 shows the typical condition encountered in this species.

From physiological studies there is not the slightest doubt that secretion occurs in the renal tubule of the toadfish. Marshall (1930), in a comparison of the function of the glomerular and aglomerular kidney, demonstrated clearly the specificity of the toadfish kidney in preventing the elimination of glucose and ferrocyanide. Bieter (1931) has demonstrated in a series of seven experiments that the secretion pressure of the toadfish kidney is distinctly higher than the dorsal aortic blood pressure recorded simultaneously. These observations on specificity and secretion pressure, combined with the present morphological findings allow us to conclude that the brush border type of epithelium, the analogue of the proximal convoluted tubule in higher vertebrates, is unquestionably secretory in function in the aglomerular kidney of the toadfish. These findings suggest also that this secretory function of brush border epithelium is probably present, in greater or lesser degree, in the glomerular fish kidneys of more complicated structure and in the kidneys of some of the higher forms.

SUMMARY

A reconstruction is shown of an entire typical renal tubule of the toadfish. The tubules of this fish are of the aglomerular type. Down to the collecting tubule, the epithelium of the tubules possesses an uninterrupted brush border. Physiological considerations, combined with this anatomical finding, demonstrate conclusively that in the toadfish the brush border type of renal epithelium is unquestionably secretory in function.

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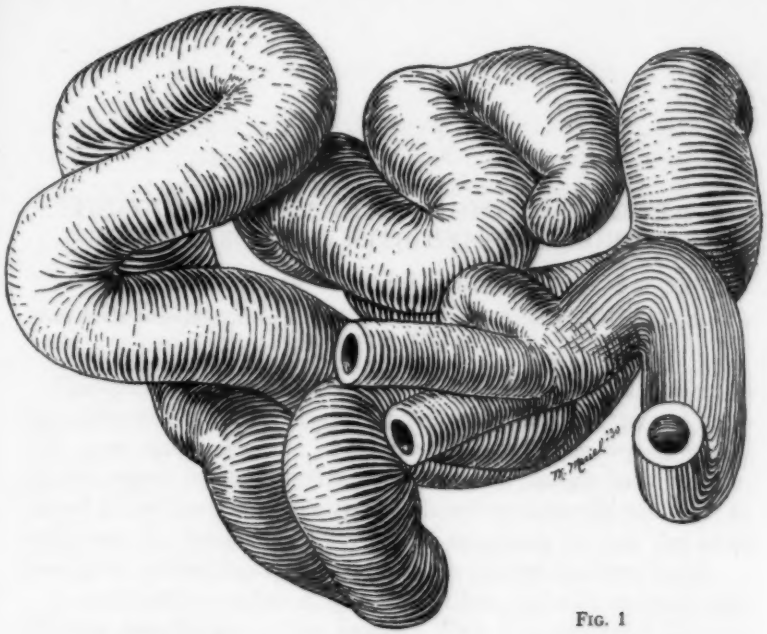

FIG. 1

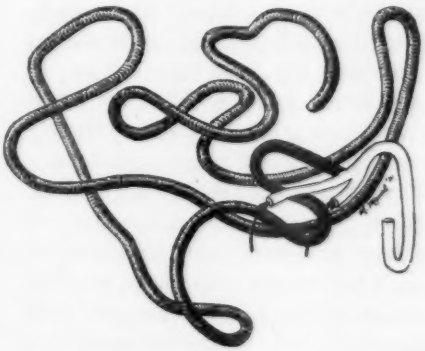

FIG. 2

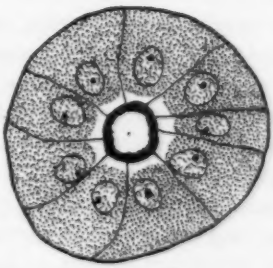

FIG. 3

FIG. 1. Drawing of wax reconstruction of typical renal tubule of the toadfish (Opsanus tau). The drawing represents one complete tubule from its blind end to its union with the collecting duct. In addition, the origins of two other tubules as they leave the collecting duct are shown.

I am indebted to Dr. George L. Streeter for his generosity in placing the facilities of his laboratory at my disposal for this reconstruction. I am indebted to Miss Muriel Maciel for the preparation of Figures 1 and 2.

FIG. 2. Schematic drawing to analyze the convolutions of the tubule in the reconstruction. The total length of the original tubule is calculated to be 2.5 mm.

FIG. 3. Typical cross-section of renal tubule of Opsanus tau, to show the nature of the brush border encountered on the distal portions of the epithelial cells. × 750.

A STUDY OF THE MORBID ANATOMY OF HEARTS FROM PATIENTS DYING WITH HYPERTHYROIDISM

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From the Cardiographic Laboratory and the Department of Pathology of the Johns Hopkins Hospital and University

The opinion is popularly held that the severe cardiac phenomena in hyperthyroidism are due to a specific toxic action of the thyroid secretion upon cardiac muscle. This view is based upon several widely quoted reports in which striking morphological changes have been observed in the hearts of people dying with or from hyperthyroidism. In reviewing the literature, however it is surprising to note the small number of reliable reports upon which this concept has been based.

A considerable number of communications deal with isolated cases showing conspicuous cardiac lesions. Thus Goodpasture's (21) two cases, which exhibited myocardial necrosis, are referred to frequently as indicating a specific effect of hyperthyroidism on the heart. Cabot (8), on the other hand, has published two cases, even better substantiated clinically, in which the hearts were normal, despite sieges of hyperthyroidism extending over 2 and 8 years, respectively. Furthermore, little attempt has been made in the earlier papers to distinguish between the various types of goitre or to submit sufficient evidence that hyperthyroidism has existed. Indeed, in some instances cases of simple colloid goitre have been frankly included. Attempts to determine the incidence of myocardial changes in a series of controlled cases have been relatively few and the results contradictory. In but one out of six cases Pettard (41) found minor alterations, and Simmonds (49) in one out of eight. On the other hand, Fahr and Kuhle (15) report lesions in 28 out of 29 cases. Such varied opinions can be accounted for only by gross differences in selection of material and in the interpretation of results. For this reason, and because the majority of reports have appeared in German and French publications, considerable space will be devoted to a discussion of the literature. It is unfortunate that

[1] Jacques Loeb Fellow in Medicine.

no extensive study has been made in this country where so much material has been available.

LITERATURE

Although the frequent association of severe cardiac disturbances and goitre had been noted by a number of clinicians following Parry's (40) classical communication, little attempt was made to investigate the relationship until 1877 when Rose (47) championed the belief that tracheal obstruction was responsible for death in such cases. Kraus (29), in a series of papers between 1889 and 1906, established the thyrotoxic heart as an entity, and pointed out that rapid and forceful heart-beat could occur in the absence of tracheal obstruction. Numerous European writers, even up to the present (39, 51, 13, 4), assume that the cardiac disturbances are due to pressure by the enlarged thyroid gland upon the trachea, the great vessels, or the vagus and sympathetic nerves in the neck. That cardiac enlargement, and sometimes circulatory failure, may result from such mechanical causes cannot be denied. We have observed one instance (U. 9451) at the Johns Hopkins Hospital in which there was enlargement of the heart and congestive heart failure associated with a massive obstructing goitre. There was neither clinical nor microscopic evidence of hyperactivity of the gland.

Furthermore, cardiac enlargement is not an uncommon finding in the endemic goitre areas of Switzerland where large tumors are relatively common (55). Bircher (6), in reviewing 196 cases of goitre that showed cardiac complications, concluded that the latter were of mechanical origin in 48 instances. Dr. Marine has shown one of us (D. M.) a specimen from a sheep with a large colloid goitre, exhibiting great hypertrophy and dilatation of the heart, aorta and carotid arteries. This phenomenon is observed in all animals in association with large simple goitres (35). In this connection it is of great interest that, as Bircher (5) has pointed out, a large proportion of the early papers supporting the mechanical theory of "Goitre Heart" came from Bavaria, Switzerland and the Tyrol where large colloid goitres are common. The so-called "Goitre Heart" must not be confused, as many writers have done, with the "Thyrotoxic Heart"—a distinction made by Kraus many years ago. It is with the latter that we are concerned in this paper.

The theory that mechanical alterations resulting from the enlarged thyroid gland are primarily responsible for the cardiac phenomena of hyperthyroidism has met with little favour in this country, where some form of intoxication or simple overwork is generally considered to be the important factor.

It has also been suggested that the great widening of the thyroid vascular bed in large goitres produces a structural change in the form of an arterio-venous shunt quite aside from any factors of pressure. Some credence must be granted this conception in view of the cardiac phenomena known to occur with some arterio-venous aneurysms (44, 45). Boas (7) in this country, believes that this factor, together with the increased work incident to a heightened metabolism, is responsible for the cardiac changes in exophthalmic goitre. That such a factor is not the important one in this disease seems probable in view of the following facts:

1. Cardiac hypertrophy, arrhythmias and decompensation occur not infrequently in hyperthyroidism associated with a thyroid gland normal in size or only slightly enlarged, and exhibiting few signs of a widened vascular bed or increased blood flow.

2. Following partial lobectomy or ligation of the thyroid arteries no immediate circulatory improvement occurs such as may be observed when an arterio-venous aneurysm is tied.

3. Recent experimental work (33) has shown that the hearts of of hyperthyroid animals, even when completely isolated, *exhibit a persistent greatly enhanced rate.* This suggests some fundamental change in the metabolism of the cardiac tissue (2, 37).

It would appear that cardiac disturbances resulting purely from mechanical factors are relatively rare, save in those areas of endemic goitre where large colloid growths are seen. Chvostek (12), in his excellent monograph, expresses the opinion that no purely mechanical form exists. Certainly in this country cardiac disturbances of thyroid origin are seldom seen save in association with hyperthyroidism.

Numerous observers have described pathological changes in the hearts of patients dying with hyperthyroidism. Askanazy (3) reported brown pigmentation, fatty degeneration and interstitial myocarditis. Matti (36), in a study of 10 cases, found localized fatty infiltration, nuclear changes and fragmented muscle fibres in 2 out of 3

instances in which microscopical sections were made. Chrustalew (11) described traces of parenchymatous alteration in 7 cases. Pettavel (43), in a very satisfactory report of 8 cases, noted varying degrees of fatty infiltration in every instance.[2] Myocardial scarring was observed in only one case—a patient of 49, with atheroma of the aorta and coronary arteries. Fatty infiltration of the skeletal muscles occurred in 6 cases. In no instance was cellular infiltration or necrosis of the myocardium observed. The author believed that the metabolism of the muscle fibres had been seriously disturbed by the action of some toxic substance.

In striking contrast are the communications of other authors. Lewis (32) has recently reported the post-mortem findings in 12 cases of hyperthyroidism from the Lahey Clinic and New England Deaconess Hospital. The hearts in 10 of 12 cases showed hypertrophy. Of the 3 instances of notable myocardial change two were apparently post-rheumatic and one was associated with thymicolymphatic hyperplasia. No specific changes were found.

Means and Richardson (38), in reporting a study of their material at the Massachusetts General Hospital, lay little emphasis on the myocardial changes and state that "the hearts, except in a few instances, showed surprisingly little hypertrophy."

Simmonds (49) in a series of 8 cases found changes in only one. These consisted of small areas of fibrosis in the musculature and slight localized fatty infiltration in the muscle fibres. The presence of pericardial adhesions suggested the inflammatory origin of these alterations. Pettard (41) found cardiac enlargement and minor myocardial changes in one out of six cases. Hezel (25) described a case of exophthalmic goitre in which cardiac decompensation occurred. At autopsy the heart was found to be enlarged, but there were no changes in the heart-muscle or blood vessels. In Cabot's two cases (8) previously mentioned, the hyperthyroidism was of long duration, and in one cardiac decompensation supervened. Careful autopsy failed to reveal any alterations in these hearts.

In 1915, Wilson (58), in reviewing 1244 autopsies at the Mayo Clinic, noted that 71 per cent of *all* patients with *goitre* exhibited myocardial

[2] Similar changes were found in 3 of 4 cases reported earlier by the same author (42).

changes visible to the naked eye as opposed to 44 per cent of cases of cancer, 48 per cent in diseases of the genito-urinary organs and 60 per cent in cases of syphilis. When the hearts of 100 cases of "goitre" were studied, gross or microscopic changes were found in practically every instance. Fatty degeneration was the most common histological finding—often sharply delimited to individual fibres or groups of fibres and seen most frequently in the middle of circumferential laminae or immediately beneath the endocardium. A more complete report was promised but has not appeared.

Willius, Boothby and Wilson (57), in 1923, mentioned briefly the necropsy findings in 22 cases of exophthalmic goiter and of adenoma with hyperthyroidism. The heart was greatly hypertrophied in 2 instances, and in 14 (in 11 of which the patients were over 45 years of age) there was an increase in heart weight of 5 to 10 per cent. The hearts in 18 of the 22 cases showed "swelling and lipoid changes" in the muscle fibres; since only 5 of these patients were under 40 years of age, the authors considered it difficult to draw satisfactory conclusions. Again, no detailed data were given. Their opinions were summarized as follows:

"At necropsy insufficient evidence is disclosed to ascribe death to cardiac causes. Although in most cases degenerative changes were found, they could not be considered the dominant factor producing death. The finding of fatty degeneration of the heart, which in some cases is no more than that found in persons who die of old age, appears to be an expression of the effect of a long continued or intense toxaemia, combined with increased activity."

The most comprehensive report is that of Fahr and Kuhle (15), who reviewed 27 cases in some detail—18 of exophthalmic goitre[3] and 9 of adnomatous goitre. Eleven of the total number were under 40 years of age. In 15 out of 18 cases of exophthalmic goitre and in 8 out of 9 cases of adenomatous goitre, hypertrophy, dilatation, and a glazed appearance of the muscle fibres were apparent to the naked eye. Irregularly distributed degeneration of muscle fibres with newly formed fibroblasts and resulting patches of fibrous tissue of varying age was demonstrable microscopically. The intensity of the lesions varied

[3] Five of these cases were reported more fully by Fahr (14) in 1916; in one, showing lymphocytic infiltration of the myocardium, the patient had died of paratyphoid fever.

from insignificant ones to extreme diffuse changes in different cases. Only one case of the total number failed to show, in some degree, the alterations described above. The conclusion was reached that some toxic substance had produced a direct effect upon the heart, but great emphasis was laid upon the fact that the lesions could by no means be considered specific.

Extreme changes resembling necrosis of the heart muscle were first described in 1916 by Fahr (14) whose two patients (each *aet* 21) exhibited localized areas of fragmentation, hyaline degeneration, and lymphocytic infiltration between the fibres and around the vessels. Fatty infiltration was minimal. In 1921 Goodpasture (21) published his two cases which showed local areas of necrosis and marked interstitial oedema, but little evidence of cellular reaction. The first patient also had syphilis. Goodall and Rogers (19) found scattered areas of necrosis in the heart of a patient, *aet.* 21, who had died of thyrotoxicosis. Infiltration of lymphocytes and endothelial cells had already commenced in these areas.[4] Similar, but less marked, lesions were found in a woman of 51. Although the authors claim (*B.M.J.* 1927) to have seen 8 additional instances, no further reports have appeared in the literature. Ceelen (10) also observed instances of this profound alteration. The conclusions drawn from the two recently reported cases of Wegelin (56) would scarcely seem admissible. In the first case a large thrombus extended up from the femoral artery through the aorta and into the heart, where it became adherent to a papillary muscle. The lesions were found beneath this area of adhesion. The second case apparently terminated by a blood-stream infection. Loos' (34) case, which appears valid, exhibited scattered necrotic lesions in varying stages of breakdown and repair, lymphocytic infiltration and scar-tissue formation. Goodpasture, Goodall, Loos and Wegelin point to the ventricles as being more usually affected.

That hyperthyroidism frequently brings about cardiac hypertrophy seems beyond dispute. Practically all autopsy studies agree on this point (15, 43, 25, 57, 49), although they may disagree upon the associated histological changes. In addition, a large number of careful observations, Hoskins (26), Hewitt (24), Cameron and Carmichael (9),

[4] This case is also reported in the *Brit. Med. Journ.*, I, 1141–1142, June 25, 1927, where the illustrations are considerably better.

Hashimoto (23), Simonds and Brandes (50), have confirmed Iscovesco's (27) original finding that experimental hyperthyroidism in animals results in cardiac hypertrophy. The morbid histology of hearts from thyrotoxic animals has not been studied so extensively and the evidence is less certain.

In 1921, Hashimoto (23), who had observed lymphocytic infiltration in the hearts of 2 cases of exophthalmic goitre, was led to make an extensive study of the effect of experimental hyperthyroidism on the morphology of the rat's heart. Thirty-eight animals were fed toxic doses of thyroid substance (0.1 to 0.5 gm. daily); ten of these died and 28 were killed with chloroform (See Goodpasture—*Loc. cit.*). Of those fed 0.5 gm. daily, 90 per cent, and of those fed 0.3 daily, 50 per cent exhibited lesions characterized by swelling and separation of muscle fibres, but without fatty degeneration. There were localized areas containing lymphocytes, fibroblasts and large mononuclear cells. These were seen most frequently around blood vessels or under the pericardium, and their resemblance to Aschoff bodies was noted. Of 11 animals fed non-toxic doses (0.03 gm. every other day) 4 exhibited similar changes but none of the 36 control animals showed comparable lesions.

In the same year Goodpasture (20) published the results of a similar study on rabbits. Seven animals were fed thyroid gland (1 gm. daily for from 15 to 26 days) and a similar number were injected intravenously with thyroxin (1.0 mg. every other day for from 9 to 23 days). Numerous sections were made from each heart. The auricles showed no abnormality. "Definite but insignificant" changes were found in the ventricles, consisting of perivascular fibrosis and small areas of fibrosis or atrophy at the base of the papillary muscles. Fifteen animals, given similar quantities of thyroid material were, after 2 to 23 days, subjected to chloroform inhalation for one hour and killed 24 to 72 hours later. Areas of necrosis were found in the ventricles of all but 3 animals. Mononuclear infiltration was present in the first 24 hours but rapidly disappeared, leaving only fibroblasts after 96 hours. The auricles were unaffected and the livers showed no lesions.

Goodpasture concluded: "The evidence does not indicate that products of the thyroid alone could be entirely responsible for the cardiac lesions which may occasionally occur in man in association with

hyperthyroidism." He felt that hyperthyroidism probably weakened the resistance of the myocardium to toxic agents.

Cameron and Carmichael (9) found no histological changes in the hearts of rats that had been fed thyroid gland over long periods of time. The obvious conflict between the evidence of Hashimoto and of Goodpasture remains unexplained. That rats and rabbits should exhibit a different histological response to hyperthyroidism seems unlikely, nor does it seem possible that the chloroform, with which Hashimoto killed the majority of his animals accidentally reproduced Goodpasture's experiments.

Takane (52) fed thyroedin (0.004–0.08 gm. per 50 gm. wt. daily) to rats, guinea-pigs and rabbits, and noted myocarditis, with round-cell infiltration of the wall of the ventricle, which appeared about the 7th day and was most marked about the 12th day. Sodium iodide and potassium iodide were found to have the same effect. The author (53) assumed—[from the figures of Furth (18) and Riesenfeld (46)]—that the heart contained more lactic acid than any other organ and that this substance released free iodine from its salts, thus causing a myocarditis. The results of Furth and Riesenfeld are not applicable to the case, however,[5] and Takane's explanation, although frequently quoted, must be regarded as fanciful.

Rake and McEachern[6] have recently made a study of the pathological changes in the hearts of animals rendered hyperthyroid with thyroxine. Forty-four rabbits and 17 guinea-pigs were given intramuscular injections of thyroxine every other day and sacrificed at varying intervals. Tissues from a series of normal animals (20 guinea-pigs and 43 rabbits) were examined as a control. The changes in the heart and other tissues of hyperthyroid animals were insignificant and varied but little from changes seen in normal control animals. Of 8 thyrotoxic guinea-pigs that developed coincidental infection (bronchisepticus) all showed myocardial lesions. Of 9 thyrotoxic guinea-pigs, free of infection, only one gave evidence of myocardial change. It was considered that no significant alterations had been produced by the hyperthyroidism.

[5] See Andrus *et al.* (2) and Katz and Long (28).

[6] Rake, G., and D. McEachern: Experimental Hyperthyroidism and Its Effect upon the Myocardium in Guinea-pigs and Rabbits. *Jour. Exp. Medicine.* In Press.

A review of the available evidence leads to several conclusions:—*viz.* Mechanical factors are rarely responsible for the cardiac phenomena in hyperthyroidism. Cardiac hypertrophy results frequently from hyperthyroidism both in clinical cases and also in experimental animals. It is obvious also that extraordinary contradictions appear in the evidence submitted by different observers concerning the morphological changes in the hearts of patients dying with hyperthyroidism. The balance of opinion would suggest that myocardial scarring, infiltration of small round cells and minor degenerative changes are to be found frequently. Some workers have failed to find these alterations. It is certainly true that no lesions of a specific character have been described.

Isolated instances of profound, acute changes have been described (Fahr, Goodpasture, Goodall, etc.) but are apparently very uncommon. Equally profound alterations have been reported in conditions totally unrelated to hyperthyroidism. Indeed in a number of instances no cause whatever has been ascertained for conspicuous alterations in the heart (17, 16, 48). No adequately controlled study of a series of cases has yet been made.

METHOD

A study was made of all the cases of hyperthyroidism coming to autopsy in the Johns Hopkins Hospital since its opening in 1889. Thirty-seven cases were found in which there was conclusive evidence that hyperthyroidism existed. Ten cases were discarded because tissues or sections were not available. In the remaining 27 cases the microscopical sections were studied in each instance and the very full autopsy protocols were consulted. When Kaiserling-fixed gross specimens were available, these were examined and further microscopical sections prepared. Whenever possible fat-staining was done. The routine sections were stained with haemotoxylin and eosin. When possible, sections were taken from all chambers of the heart. When only one section was available this invariably included a portion of the left ventricular wall, mitral valve and left auricular wall. Sections from other organs were examined and positive findings were recorded.

An attempt has been made to supply sufficient clinical and pathological description to enable the reader to come to his own conclusions.

No formal differentiation has been made between exophthalmic goitre and adenoma with hyperthyroidism, although material is given in the protocols by which this distinction can be made.

Twenty-five control cases were selected, according to age, for each of the six decades (10 to 70 years) in which the cases of hyperthyroidism were scattered. These 150 cases were chosen consecutively from the autopsy records—omitting cases of goitre, syphilis, profound anemia, septicemia, pyaemia and local disease in or around the heart, (*e.g.*, rheumatic endocarditis, pericarditis, empyaema, etc.). Those cases in which coronary sclerosis was mentioned in the protocols were also discarded. In most instances death was due to accident, operative shock, intracranial lesions or local infection remote from the heart. Microscopical sections from the myocardium were examined in each case.

DISCUSSION

The cases may be divided into three groups according to the degree of alteration observed in the hearts.

I. Hearts showing no changes

Fourteen of the total series fall into this category and exhibit no changes of a kind or degree not to be found in the control groups of similar age, or which are not well recognized as occurring in general autopsy material in the absence of specific heart disease.

II. Hearts showing doubtful or moderate changes

This group contains 8 of the total series and includes those cases in which cell infiltration occurred or in which areas of intermuscular scarring or increased perivascular connective tissue were found. In several instances alterations in the staining reactions or contours of the muscle fibres occurred to a moderate degree. Changes similar to these in kind and degree were found in some hearts of the control series although not with quite the same frequency. Such hearts, in the control series, had given no indication of disturbed function during life. An evaluation of the significance of the lesions found in Group II is not without difficulty. Because of their non-specific character and their occurrence in numerous control cases it seems impossible to ascribe to

them the production of the cardiac phenomena of the disease. It is also true that, with the exception of small-round-cell infiltration, which was most common in the second decade,[7] these changes were seen more constantly in the later decades of life in both experimental and control groups. As a result of prolonged overwork and in the

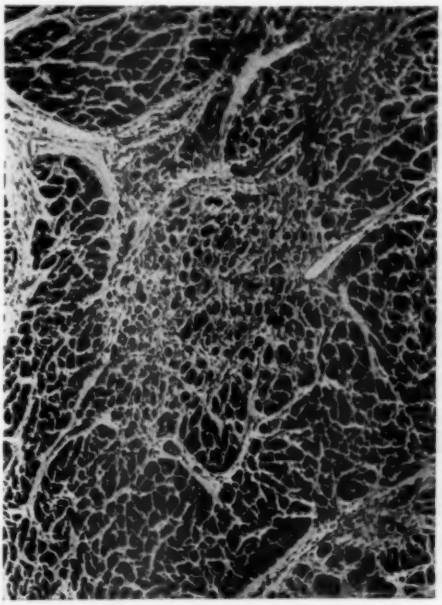

FIG. 1. Microphotograph (×50) from myocardium of a woman *aet.* 23 (A. No. 8857 of control group) who died of hyperemesis gravidarum. Intermuscular and perivascular scarring with a scattering of mononuclear cells.

presence of profound metabolic changes in the tissue (2, 33, 37) it is conceivable that alterations of this character might ultimately appear.

Too much importance has been placed by some observers upon le-

[7] Fahr and Kuhle (15), Matti (36) and Pettavel (43) give an interesting discussion of the possible relationship between small-round-cell infiltration and thymico-lymphatic hyperplasia.

sions that may be found in the hearts of patients who have given no evidence of cardiac disability during life. These changes occur with sufficient frequency to warrant some criticism of too restricted a concept of the "normal." In like manner insufficient attention has been paid to the possible co-existence of organic heart disease (*e.g.*, coronary

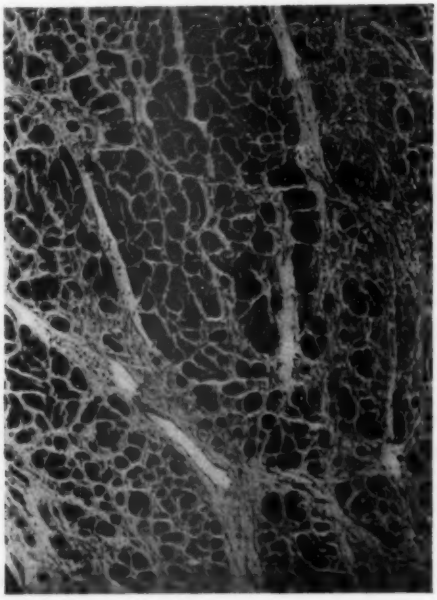

FIG. 2. Microphotograph (×50) from myocardium of a woman *aet.* 41 (A. No. 9349 of control group) who died with pneumonia of one week's duration. Marked perivascular and intermuscular fibrosis with atrophy of muscle fibres.

sclerosis, syphilitic aortitis, rheumatic endocarditis) that might account for the lesions found at necropsy.

Figures 1, 2 and 3 illustrate these points. Figure 1 is taken from the myocardium of a woman of 23 (A. No. 8857 of the control group) who died of hyperemesis gravidarum. There is definite intermuscular and perivascular scarring with a scattering of mononuclear cells. There were no cardiac symptoms during life and no evidence of cardiac

disease. The Wassermann reaction was not recorded. Figure 2 shows a section from the myocardium of a woman of 41 (A. No. 9349 of the control group) who died with pelvic abscess and pneumonia of one week's duration. Very pronounced intermuscular and perivascular fibrosis was found, with atrophy and disappearance of muscle fibres in these areas. There was nothing suggestive of syphilis at

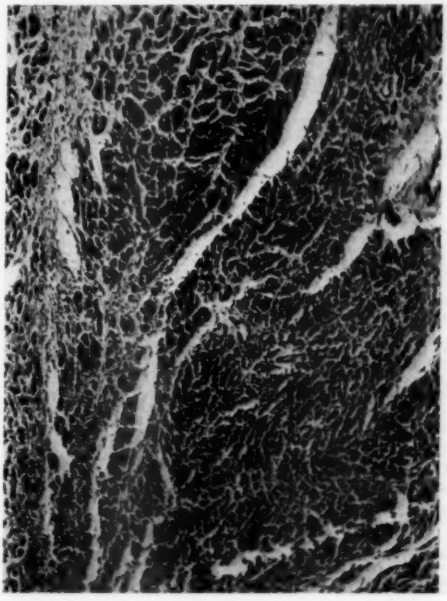

FIG. 3. Microphotograph (×50) from myocardium of a woman *aet.* 43 (A. No. 7076 of the series with hyperthyroidism). Marked diffuse fibrosis and cell infiltration. The blood Wassermann reaction was positive, and syphilitic aortitis was found at autopsy.

autopsy, nor had there been any evidence of cardiac disability during life. Figure 3 is from No. 7076, of the series with hyperthyroidism, placed in Group III because of marked diffuse fibrosis and cell infiltration found in all chambers of the heart. The Wassermann was positive, however, and autopsy showed syphilitic aortitis which may account for the changes observed.

In like manner Figures 4 and 5 demonstrate the same point with regard to infiltration of small round cells. Not infrequently such alterations are to be found in the myocardium of patients who have died from various unrelated causes and who represent the general autopsy material of the hospital. Figure 4 is from a man of 66 (A. No.

FIG. 4. Microphotograph (×190) from myocardium of a man *aet.* 66 (A. No. 9596 of control group) who died with bronchopneumonia. Several areas of small-round-cell infiltration similar to this were found. There were no cardiac symptoms during life.

9596 of the control series) who died of carcinoma of the pancreas and bronchopneumonia. Several areas similar to this were found. There were no cardiac symptoms, no coronary sclerosis and the Wassermann test was negative. Figure 5 is from No. 6600 of this series, a girl of 14 with Graves' disease of six weeks' duration. This was the only area of

cellular infiltration noted. Again the similarity is obvious. All the above sections were taken from the left ventricle, deep in the wall.

III. Hearts showing marked changes

Five cases in the whole series fall into this group and exhibit profound changes. As will be seen from the protocols, the lesions (with

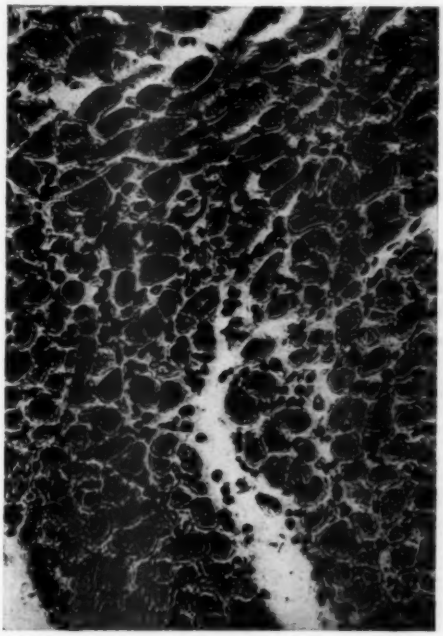

FIG. 5. Microphotograph (×315) of myocardium of a girl *aet.* 14 (A. No. 6600 of series with hyperthyroidism) who died with Graves' disease of 6 weeks' duration. This was the only area of cell infiltration noted.

the exception of those in No. 9367) consisted of areas of destruction of muscle fibres with replacement by connective tissue, infiltration of small round cells and large monocytes and, occasionally, polymorphonuclear leucocytes. Old intermuscular and perivascular scars were sometimes seen. Three of the five appeared to have co-existing

organic heart disease which might be held accountable for the lesions. In no. 7076 there was typical syphilitic aortitis, the aorta was dilated and the Wassermann test of the blood was positive. In no. 4154 there was an organized pericardial exudate, and disintegrating antemortem thrombi in the auricle, and small verrucose vegetations were

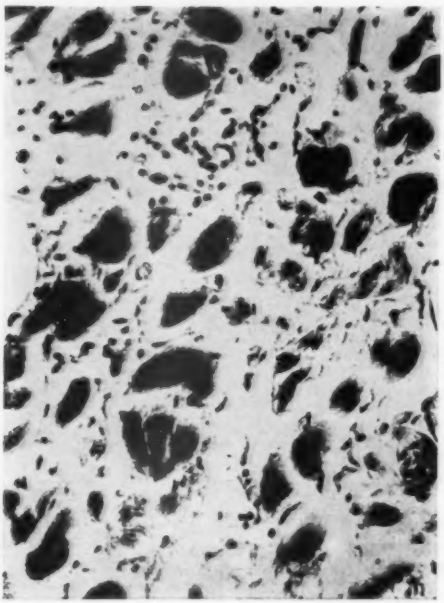

FIG. 6. Microphotograph (×315) of myocardium of a man *aet.* 57 (A. No. 9367 of series with hyperthyroidism) who died with Graves' disease and lobular pneumonia. Extreme diffuse destruction of muscle fibres and infiltration of mononuclear cells.

found on the mitral cusps. No. 8931 showed Aschoff bodies and other changes characteristic of an acute rheumatic infection. In the remaining two cases (nos. 8931 and 9367) nothing was found to account for the lesions.

No. 9367 is notable because of the extreme diffuse changes which had occurred. A microphotograph is seen in Figure 6. The picture

bears no resemblance to the focal necrosis described by other writers. This patient had had pleurisy with effusion and had died without congestive heart failure.

We have not met with focal necrotic lesions of the type described by Goodpasture, Goodall, and others.

Table I indicates the frequency of the commoner changes in the control and experimental groups.

TABLE I

Autopsy findings in hearts from 27 cases of hyperthyroidism and 150 controls

AGE GROUP	NUMBER OF CASES	INTERMUSCULAR SCARS				PERIVASCULAR SCARS				CELL INFILTRATIONS				B.A. GRANULES*			
		+++	++	+	−	+++	++	+	−	+++	++	+	−	+++	++	+	−
10–20	1											1					1
21–30	2												1				2
31–40	12		1	3	4	1	1	1	2		2		3	1	4	4	3
41–50	5	1		1	1	1	1	1	2		2	2		1	4		
51–60	5	2		1	2		2		1	1	1	1	1	1	3	1	
61 and over	2			1	1							1		1		1	
Normal controls																	
10–20	25			1	2		1	1	4			7				9	15
21–30	25		1	2			2		7			2			2	14	8
31–40	25		3	4	2		3	4	4			2			7	12	5
41–50	25	1	1	6	1		2	4	7			2†		3	12	7	3
51–60	25		5	8		1	4	3	4					2	10	13	
61–70	25	1	8	6	1	1	6	6	2			5‡		10	12	3	

* The lipochrome granules associated predominantly with brown atrophy of the heart.

† Polymorphonuclears in one instance.

‡ Polymorphonuclears in three instances.

Table II brings together the important clinical material in relation to the changes found at autopsy.

It seems to be well established that prolonged hyperthyroidism results in cardiac hypertrophy of some degree; but this of itself does not necessarily indicate myocardial damage. From the autopsy protocols it appears that hypertrophy occurred in 16 of the 27 cases. Dilatation was found frequently and probably explains the definite enlargement

TABLE II

Summary of clinical and autopsy findings in 27 cases of hyperthyroidism

AUTOPSY NUMBER	AGE	DURATION OF HYPERTHYROIDISM	AURICULAR FIBRILLATION	MODE OF DEATH	ENLARGEMENT, CLINICAL	HYPERTROPHY, AUTOPSY	CONTRIBUTORY DISEASE	GROUP*
4982	35	1 yr.	+	Operative				1
5070	28	6 yrs.	Flutter +	Toxic (post-op.)				1
5149	47	1½ yrs.	+	Toxic (post-op.)				1
5708	32	4 yrs.	−	Toxic				1
6307	30	1 yr.	−	Bronchopneumonia			Thrombus in right ventricle	1
6382	40	?	−	Toxic				1
6418	36	6 mos.	−	Air embolism (operative)				1
6600	14	6 wks.	?	Toxic				1
8103	60	1 yr.	−	Congestive failure	+	+		1
8233	54	8 mos.	−	Toxic	+	+		1
8808	61	4 yrs.	+	Congestive failure	+	+	Arteriosclerosis	1
10151	49	15 mos.	+	Congestive failure, sudden death	+	+	Died, coronary thrombosis	1
11175	63	4 yrs.	−	Toxic (post-op.)	+	+		1
11483	36	1 mo.		Toxic (post-op.)				1
2079	42	4 yrs.	+	Congestive failure	+	+	Syphilis. Heart trouble, 6 yrs.	2
6403	34	6 mos.	−	Toxic (post-op.)				2
7510	35	5 mos.	−	Toxic	−	−		2
7554	39	1 yr.	−	Toxic	+	+		2
9333	56	2 yrs.	−	Toxic, fracture femur				2
9471	35	7 mos.	+	Congestive failure	+	+		2
10344	46	5 mos.	−	Toxic	−	−		2
11604	33	1½ yrs.		Operative				2
4154	39	3 yrs.	−	Congestive failure	+	+	Organized pericarditis. ? Rheumatic	3
7076	43	8 mos.	−	Congestive failure, sudden death	+	+	Syphilis. Possible rheumatic fever	3
8145	54	6 mos.	−	Toxic				3
8931	35	6 yrs.	+	Toxic	−	−	Rheumatic endocarditis	3
9367	57	3 mos.	+	Toxic (post-op.)	+	+		3

* Division into groups was made according to pathological changes observed.

encountered clinically in nearly all of the 27 cases. In considering the pathological changes no further allusions will be made to hypertrophy and dilatation, and alterations, when spoken of, will signify changes in the structure of the heart.

No satisfactory correlation can be made between the clinical symptoms and the structural changes in the heart. Thus, of the 7 patients who died with congestive heart failure 2 showed marked changes (III), 2 moderate changes (II) and 3 were normal (I). If congestive failure is considered to be evidence of severe cardiac damage, then it must be pointed out that 5 of the 7 showing congestive failure exhibited very moderate or no cardiac change, while only 2 showed striking alterations, in both of which other cardiac disease was also present (syphilis, arteriosclerosis, rheumatic endocarditis). This brings up the whole question of the adequacy of the clinical criteria upon which our concept of cardiac damage is based. No careful observer can have failed to be impressed by the rapidity with which serious manifestations of cardiac embarrassment in hyperthyroidism may vanish, literally over night, following a post-operative storm or a satisfactory response to therapy. Extreme dilatation, tachycardia and overactivity may abate within a period of time too short to allow conceivably of corresponding reparative changes if organic lesions be held responsible. It is doubtful, too, if many of the reported deaths from "heart failure" deserve to be labelled as such more than death from any lethal infection or fever. As Hamilton (22) has shown, the majority of patients who die from hyperthyroidism are driven to death by the disease without ever developing congestive heart failure. This is certainly true in our series. One usually wonders how the heart manages to keep going so long when the patient is moribund and almost "burned out." Certainly there seems little excuse for perpetuating the latter part of Moebius' text—"Basedow patients suffer and die through their hearts." That profound alterations in the function of the heart have occurred is perfectly evident but that structural and, therefore irreparable, changes must be held accountable, does not necessarily follow.

Most patients who die with hyperthyroidism die the so-called "toxic" death. The pulse rate gradually rises, delirium sets in, respirations become rapid and the temperature goes up, often to 106° or 108°F. Out of the 25 patients in this series 15 died in this manner.

This may occur either before operation can be attempted or within the first few days following operation. The hearts in this group of 15 cases showed changes in no way different from those found in the group dying with congestive failure save that coexisting cardiac disease (*viz.* rheumatic endocarditis, etc.), was more common in the latter group. Of the six instances in the entire series in which coexisting cardiac disease was found, 5 had congestive failure and one (No. 8931) died a toxic death. This is in accord with the statistics recorded by Andrus (1) who has shown that, when congestive failure appears in hyperthyroidism, there is usually some other organic factor (*e.g.*, rheumatic endocarditis, syphilis of the heart or aorta, arteriosclerosis or advancing age) which tends to lower the cardiac reserve. This fact is of real clinical importance, for after the added burden of hyperthyroidism has been removed by adequate treatment, the heart is often able to perform satisfactorily under the reduced load and compensation is restored. The excellent reports of Hamilton (22), Levine (31), Lahey (30) and others testify to this point and Thomas has recently published another interesting example (54).

Nor can it be said that auricular fibrillation necessarily indicates any structural alteration in the heart. Certainly, in the laboratory fibrillation can be produced with ease (*e.g.*, by asphyxia) without the necessity of producing structural damage to the heart. It is quite possible that its occurrence in hyperthyroidism is often on a functional basis. It usually disappears following relief of the hyperthyroidism provided there is no coexisting organic heart disease. In this series myocardial lesions were found less often, if anything, in the cases with auricular fibrillation than in those with a normal rhythm.

The duration of symptoms of hyperthyroidism bore no relationship to the changes found after death, as will be seen by reference to Table 2. From the evidence submitted it would appear that there is little justification for considering that the heart is directly attacked by a destructive toxin or poison. There is certainly no basis for the term "thyroid myocarditis" which is still found frequently in textbooks and articles on the subject. Whether or not the functional changes in the heart in hyperthyroidism render the myocardium more susceptible to injury by toxic agencies is not yet proven by the available evidence.

Finally, we wish to emphasize the desirability of further studies of

the functional changes in the heart in hyperthyroidism. It is felt that such are more likely to prove productive than further investigation of the structural changes. A possibility exists that the heart and perhaps all muscular tissues, or even all tissues of the body, undergo some profound metabolic disturbance in hyperthyroidism. Well controlled clinical and physiological experiments should throw much light on the subject.

SUMMARY

The literature on the pathology of the heart in hyperthyroidism is reviewed and the contradictions of evidence are pointed out and discussed. Twenty-seven cases of patients dying with hyperthyroidism are reported with clinical and pathological notes. The cardiac findings are compared with those in 150 suitably chosen control cases.

In 14 instances the hearts were normal. In 8 instances moderate perivascular or intermuscular fibrosis or small-round-cell infiltration was found; similar changes were also encountered among the control cases, though less frequently. Conspicuous alterations were found in 5 instances, in 3 of which there was co-existent heart disease. Cardiac hypertrophy was noted in 16 of the 27 cases. No relationship could be established between the incidence of auricular fibrillation or the duration of hyperthyroidism and the ultimate findings in the heart. Congestive heart failure occurred in 5 of the 6 cases that presented co-existing organic heart disease. From this evidence it is impossible to ascribe the cardiac phenomena of the disease to structural changes in the muscle. It is pointed out that the hearts from hyperthyroid animals continue to beat, when isolated, at a much faster rate than similar preparations from normal animals. Emphasis is placed upon the desirability of studying the problem from the viewpoint of metabolic and functional alterations in the myocardium.

CASE HISTORIES

E. S. A. No. 2079. S. No. 14215. W. F. *Aet.* 42. Admitted January 2, 1903. Died February 26, 1903.

F.H. One sister died of rheumatic fever.

P.H. Frequent pneumonia. 6 or 7 haemorrhages from lungs. No tuberculosis found. Dropsy one year ago; eyelids, legs and abdomen affected. Syphilis with treatment during early married life.

P.I. Doctor told her six years ago "trouble with heart." Four years ago eyes commenced to get prominent and she noticed palpitation, dyspnoea, tremor of hands and swelling of neck. Occasionally heart goes so fast—can't count. Usual rate 108.

P.E. P. 120. T. 98.6°F. R. 20. Emaciated, nervous. Definite exophthalmos. Classical eye-signs. Thyroid moderately and symmetrically enlarged and soft. No thrill nor bruit. Fairly dyspnoeic. Lungs negative. Heart: P.M.I. in 5th space, nipple line. Systolic murmur at apex. Pulse 140 to 160, totally irregular. Urine, negative. Pulse sometimes regular at 110 to 120. Other times irregular at 160 to 170. Course—down hill. Cyanosis. Ascites appeared. Died on February 26th with T. of 106°F.

Impression. Exophthalmic goitre.

Autopsy. 2¼ hours post mortem. The heart is slightly enlarged but no actual weight is given. The wall of the left ventricle is 10 mm. thick. The mitral valve shows a slight degree of general thickening and a few minute verrucose vegetations. Microscopically, there is quite definite perivascular scarring and some finer intermuscular fibrosis with a few mononuclear cells. Brown atrophy pigment granules are prevalent. The vegetation on the mitral valve is organized. The thyroid. microscopically, shows small acini lined by high columnar epithelium with numerous folds projecting into the lumen. The acini contain very little colloid. Lymphoid tissue in the form of small nodules is present between the acini in many places. The thymus is hyperplastic. Both spleen and liver, but especially the latter, show chronic passive congestion.

R. G. A. No. 4154. M. No. 30642. F. C. *Aet.* 39. Admitted June 20, 1914. Died July 11, 1914.

F.H. Negative.

P.H. "Rheumatism" for several years. Alcohol ++.

P.I. Shortness of breath for about 37 months, gradually increasing, palpitation on exertion, swelling of feet occasionally in morning. On admission March 13, 1913, eyeballs noted as prominent. No eye signs or thyroid enlargement. Heart: M.D.L. 14.5. M.D.R. 3.5. Impulse +. Systolic murmur. Pulse around 100 when temperature was normal. Three months ago swelling of feet became worse, dyspnoea increasing. Orthopnoea, 1 week. Slight cough. Abdomen swollen, 1 week. Loss of weight. Sweating.

P.E. Undernourished. Quiet. Cyanosis—, icteroid sclerae, marked exophthalmos. No von Graefe. Marked increase in size of thyroid. Soft and granular. No thrill or bruit. Both lobes and isthmus involved. Lungs: moist râles in both axillae and bases. Oedema of back. M.D.L. 15. M.D.R. 4. Gallop rhythm. Rate 140, regular. First sound slapping and loud. Systolic murmur. Liver 3 cm. down. Slight edema of wrists and forearms. Fluid wave abdomen. Oedema of thighs and shins. Marked tremor of fingers. B.P. 165/75. W.B.C. 8,400. Urine, trace of albumin. Goitre increased, bruits appeared. Tachycardia increased, pulse became weaker, died—July 11, 1914.

Impression. Myocardial degeneration. Exophthalmic goitre.

Autopsy. 7½ hours post mortem. The heart weighs 350 gm. The pericardial surface shows an organized exudate. The wall of the right auricle is hypertrophied as is that of the right ventricle; both chambers are dilated and the auricle contains breaking-down thrombi. On the mitral valve are some pinhead verrucose vegetations. The wall of the right ventricle measures 9 mm., that of the left 14 mm. Microscopically, there is some loose connective tissue together with a few mononuclear cells around the blood vessels and between the muscle fibres. In places there are groups of polymorphonuclear leucocytes. Brown atrophy pigment granules are present but not increased. The acini of the thyroid are of moderate size; the epithelium high and greatly infolded. The acini contain only a little thin secretion. All the other organs show marked post mortem changes. The thymus tissue is scanty. Liver and lungs show some chronic passive congestion. The lungs, moreover, show some fresh and necrotic miliary tubercles and a few patches of lobular pneumonia.

E. J. A. No. 4982. S. No. 41533. W. F. *Aet.* 35. Admitted October 2, 1916. Died January 9, 1917.

F.H. Non-contributory.

P.H. Non-contributory.

P.I. Moderate symmetrical enlargement of neck for three years. No symptoms until one year ago when she became nervous, and swelling became larger. About January 1916, rapid increase in symptoms—nervousness, eyes became prominent, neck very large, loss of weight, fatigability. For 2 months rapid throbbing over heart, profuse sweats and swelling of feet at night.

P.E. T. 99. P. 120. B.P. 140/75. Markedly nervous. Definite exophthalmos with all classical signs, including pigmentation of body. Thyroid symmetrically enlarged, systolic thrills and bruits over both lobes. R.M.D. in second interspace—10.5 cm. Heart: Marked pulsation. P.M.I. 13.5 cm. from M.L. and forcible. Rhythm irregular. No oedema of shins. Liver down two fingerbreadths. Electrocardiogram—Auricular fibrillation. Urine negative. Under digitalis heart became smaller and pulse more regular. Despite ligation of superior and inferior thyroid vessels patient got worse; T. 98.6°–100°. Loss of weight. January 9, 1917: Right lobectomy. Respiratory embarrassment. Heart sounds disappeared. Apparently a cardiac death in face of respiratory embarrassment, anaesthetic and operation.

Impression. Exophthalmic goitre.

Autopsy. 1½ hours post mortem. The heart is not enlarged. The right ventricle measures 3 mm., the left 10 mm. Microscopically, small groups of lymphoid cells are seen in relation to several of the smallest coronary branches. Brown atrophy granules are very plentiful. The thyroid is adenomatous. The acini for the most part are of moderate size and lined with high columnar epithelium showing much infolding. They contain no colloid. There is a small separate nodule with regular round acini containing colloid. The adrenals are small but

otherwise normal. The thymus is hyperplastic. There is a definite periportal infiltration of mononuclear and lymphoid cells in the liver.

C. T. A. No. 5070. M. No. 37362. S. No. 42125. W. F. *Aet.* 28. Admitted (M.) March 4, 1917, to (S.) March 12, 1917. Died March 20, 1917.

F.H. Negative.

P.H. Negative.

P.I. Began six years ago with weakness, loss of weight, nervousness, sweating, slight enlargement of neck, and epileptiform fits definitely hysterical in type.

P.E. T. 98.2°F. P. 96. R. 20. B.P. 120/75. Apathetic, considerable loss of weight, tanned appearance, slight throbbing of jugular veins. No exophthalmos nor hyperthyroid eye-signs. Skin damp. Both lobes of thyroid moderately enlarged. Slight systolic thrill over both lower lobes but no bruit. Heart: Pulse 100, regular. Definite fine tremor of fingers. Impression: (Dr. Goetsch) mild hyperthyroidism. Pulse averages from 85 to 100. Urine negative. Wassermann negative. March 15, 1917. Double lobectomy (Dr. Halsted). Condition good. Sections colloid goitre. Developed aphonia March 16th. Pulse 190, at wrist and regular (200). Auricular flutter (Dr. Janeway, Dr. Bloomfield). Intravenous strophanthus, temporary improvement—Pulse 128, but temperature rose gradually; râles in chest, pulse uncountable. Died at 9.15 P.M. March 20, 1917.

Impression. Exophthalmic goitre.

Autopsy. 17 hours post mortem. The heart weighs 225 gm. It shows neither hypertrophy nor dilatation. Right ventricle measures 3 mm. and the left 10 mm. The coronary vessels are normal. Microscopically, there is considerable fragmentation of the muscle fibres but no other change. The thyroid shows some large colloid-filled acini with flattened epithelium and others considerably smaller or solid and lined with columnar cells. The thymus is hyperplastic. Liver, spleen and kidneys show slight chronic passive congestion. There are a few patches of lobular pneumonia.

J. S. A. No. 5149. S. No. 42758. W. F. *Aet.* 47. Admitted May 2, 1917. Died May 25, 1917.

F.H. Negative.

P.H. Non-contributory.

P.I. Dates from great fright 18 months ago. Since then progressive weakness, palpitation, enlargement of neck, nervousness, dysphonia, marked perspiration, tremor and loss of 60 lbs. in weight. Period of edema of legs during past year. Exophthalmos for two months.

P.E. T. 99. P. 114. B.P. 140/80. Emaciated, restless. Skin pigmented and moist. Moderate exophthalmos. Classic hyperthyroid eye signs. Large pendulous goitre, symmetrical but hard and granular. Systolic thrill and bruit both upper poles. R.M.D. increased. Lungs negative. Heart: Systolic shock

and heave. M.D.L. 12 cm. M.D.R. 3.5 cm. Systolic murmur all over precordium. Sounds loud. Rhythm irregular. Abdomen negative. No oedema. Fine tremor. Electrocardiogram—Auricular fibrillation. Urine negative. W.B.C. 5060. X-Ray, Substernal goitre. Rapidly became worse despite therapy. Ligation of superior thyroid arteries—May 25th. Four hours later pulse imperceptible. Respirations continued for brief time after heart had stopped.

Impression. Exophthalmic goitre suggesting malignant change in gland.

Autopsy. 18 hours after death. The heart weighs 300 gm. There is neither hypertrophy nor dilatation. The right ventricle measures 2 mm.; the left 10 mm. The coronary arteries show a few small patches of atheroma. Microscopically, there is a little edema of the intermuscular tissue. A few mononuclear cells are present around the vessels. The thyroid shows large acini with cubical lining cells and a plentiful colloid content. Fewer of the acini are small with columnar cells and no colloid. The fibrous stroma is increased and there are numerous lymphoid nodules. There is chronic passive congestion of most of the organs especially the liver. The thymus is hyperplastic. The lung shows chronic bronchiectasis and fresh acute bronchitis and lobular pneumonia.

C. F. A. No. 5708. S. No. 46571. W. F. *Aet.* 32. Admitted September 26, 1918. Died, October 2, 1918.

F.H. Negative.

P.H. Many sore throats and severe chorea in childhood. Always delicate. No rheumatic fever.

P.I. Shortness of breath for four years. Present illness dates from 14 months ago with increasing nervousness, dysphagia, weakness, loss of weight (from 118 to 89 lbs.) edema of legs, profuse sweating, rapid pulse ("twice normal") and throbbing of heart. Past 6 months, swelling of neck and exophthalmos. Hoarseness for three months. In bed for 6 months.

P.E. T. 100. P. 168. R. 24. B.P. 125/65. Much emaciated, restless, husky voice, moist skin, slight cyanosis, marked exophthalmos. Von Graefe and Stelwag positive. Isthmus and both lobes of thyroid symmetrically enlarged. Systolic thrill and bruit both lobes. R.M.D. increased. Lungs clear. Heart: P.M.I. diffuse and accentuated. M.D.L. 13.5 cm. M.D.R. 4 cm. Systolic murmur at apex. Rate 160, and regular. Abdomen negative. Electrocardiogram—Sinus tachycardia. W.B.C. 15,320. (P.M.N., 87.3 per cent) Urine—Albumin +, Acetone +, Diacetic ++. Commenced to vomit. Pulse and temperature rose. Dyspnoea became worse despite treatment. Died, October 2nd. Pulse rose to 225 but remained regular.

Impression. Exophthalmic goitre.

Autopsy. 1 hour after death. Heart not enlarged. The right ventricle measures 3 mm., the left 15 mm. The coronary arteries are normal. Microscopically, apart from slight increase in perivascular fibrous tissue no abnormality is seen. In the thyroid many of the acini contain colloid but nevertheless the epithelium is

columnar and much infolded. There is some lobular pneumonia. The liver shows a peripheral fat accumulation.

A. F. A. No. 7510. M. No. 48433. F. W. *Aet.* 35. Admitted May 16, 1920. Died May 29, 1920.

F.H. Negative.

P.H. Negative.

P.I. Five months ago commenced to get tired easily, nervous, sleepless. Irritability and palpitation and well marked dyspnoea on exertion. Coughed blood frequently. One month ago neck began to swell. Hair began to fall out; amenorrhoea; sweating troublesome. Now unable to climb steps. Mild tremor.

P.E. P. 110. T. 99. B.P. 130/70. Very nervous, sweating, fairly well developed. Wide orbital aperture and lid-lag. General thyroid enlargement, firm, no thrill, systolic bruit. *C.V.* Pulse regular. M.L.D. 9 cm. M.R.D. 3 cm. No shocks. Systolic murmur over entire heart. Abdomen and Lungs, negative. Coarse tremor of hands. B.M.R., plus 64. Rapidly became worse, excited and delirious. Moribund. Pulse 160. T. 107. Death on May 29th.

Impression. Exophthalmic goitre. Toxic Psychosis.

Autopsy. 3 hours post mortem. Heart weighs 320 gm. The right ventricle measures 4 mm. the left 15 mm. The coronaries are normal. Very fine scars can be seen in the myocardium. Microscopically, all four chambers show some degree of perivascular and intermuscular scarring which is most marked in the right auricle. The muscle fibres are atrophied but not necrotic. The brown atrophy granules are slightly increased in amount. Fat stains show no fat apart from lipochrome granules. The thyroid shows small acini without colloid and with columnar irregular epithelium. The liver shows marked chronic passive congestion. The thymus is hyperplastic. There are some areas of fresh lobular pneumonia.

A. W. A. No. 6307. Gyn. No. 26038. W. F. *Aet.* 30. Admitted June 22, 1920. Died July 14, 1920.

F.H. Negative.

P.H. Negative.

P.I. Admitted for subacute appendicitis—4-year history. Flare up last two weeks. Dyspnoea on exertion 1 year, occasional swelling of legs. Loss of weight last two weeks. No palpitation.

P.E. T. 99°F. P. 138. B.P. 175/70. R. 36. Obese, anxious, seems in pain. Skin darker than normal. Face, hands and feet markedly suffused, hands moist, fine tremor of fingers. Marked exophthalmos with eye signs; irregular, nodular enlargement of thyroid, not hard. Lungs: Negative. Heart: P.M.I. 5th space 11.5 cm. from M.L., forcible impulse M.D.L. 13 cm. Loud systolic. Action regular. Abdomen—marked tenderness and muscle guarding over right hypochrondrium. No oedema. Operation: Upper abdomen normal. Appendix thick and

red, removed. Progress stormy, pulmonary infection, pleurisy. Pulse, respiration and temperature increased gradually. Died July 14th. P. 190. T. 104. R. 68. Urine—Albumin trace, some sugar at times.

Impression. Hyperthyroidism. Thyroidheart. Bronchopneumonia.

Autopsy. 5 hours after death. The heart weighs 300 gm. The coronaries show slight sclerosis. The wall of the right ventricle is 5 mm.; that of the left 12 mm. At the apex of the right ventricle is a large crumbling thrombus. Microscopically, beneath the endocardium there is a slight mononuclear infiltration. Otherwise negative. The thyroid is adenomatous. In some places the acini, though small, are lined with flattened cells and contain colloid, in others there are groups of small immature acini. For the most part, however, the acini are of medium size, lined with columnar and infolded epithelium, and contain no colloid. Lymphoid nodules are frequent. The liver shows marked peripheral fat accumulation. In the lung there are some infarcts; the vessels leading to these contain organized thrombi. There is a little lobular pneumonia.

E. C. M. A. No. 6382. H.P.P.C. No. 2789. F. W. *Aet.* 40. Admitted October 7, 1920. Died October 25, 1920.

P.H. Negative.

P.I. No history of goitre in P.I. P.I. is concerned only with the mental state.

P.E. T. 101. P. 120. B.P. 130/78. Poorly nourished woman, stuporous expression. Thyroid visibly enlarged, with soft anterior lobe, enlarged more to the right. No exophthalmos. Von Graefe negative. Tremor of hands and fingers. Forcible extensive apex beat. Systolic murmurs heard at left sternal boarder and at apex, transmitted into the axilla. Heart enlarged 4 x 14.5. P.M.I. 5th interspace, 13.5 to left of M.S.L. No hardening of peripheral arteries. Amenorrhoea 5 months. W.B.C. 10,400. Wassermann negative. C.S.F. negative. Persistent tachycardia, slight fever with evening rise of temperature. 10/24/20. W.B.C. 18,200. Patient getting worse. Pulse 140–180. T. 105. R. 56. Died.

Impression. Agitated depression. Cystitis. Exophthalmic Goitre. Bronchopneumonia.

Autopsy. Less than 12 hours post mortem. Heart not enlarged. Both mitral and aortic valves slightly thickened. Microscopically, there is very slight fibrosis at the base of the mitral valve. Brown atrophy granules are not increased In one place there is a small subepicardial haemorrhage. Otherwise there are no abnormalities. The thyroid shows rather small acini with cubical and regular lining cells and not much colloid. A section of bladder shows a subacute cystitis.

L. P. A. No. 6418. S. No. 52316. F. C. *Aet.* 36. Admitted October 25, 1920. Died November 3, 1920.

F.H. Negative.

P.H. "Rheumatism" during last eight years, flitting from joint to joint.

P.I. Began six months ago. Lump in neck, increasing exophthalmos, nervousness, insomnia, dyspnoea and loss of weight.

P.E. T. 98.8. P. 140. R. 27. B.P. 160/60. Marked emaciation, sweating, exophthalmos (classical eye-signs). Thyroid symmetrically enlarged, soft systolic thrill and bruit. R.M.D. slightly increased. Lungs negative. Marked precordial pulsation. M.D.L. 12. M.D.R. 5. Systolic murmur at apex. Abdomen negative. No oedema. Electrocardiogram: Sinus tachycardia. Urine negative. W.B.C. 6,400. B.M.R. plus 85. X-Ray: Heart dilated in all directions. Operation. Double partial lobectomy. November 3, 1920. Died of air embolism on table.

Autopsy. 5 hours post mortem. Heart not enlarged. Both coronary arteries contained air at autopsy. The right ventricle measures 5 mm. the left 18 mm. Microscopically, apart from some very fine intermuscular fibrosis there is no abnormality. In the thyroid a few acini are normal. The majority, however, are small with columnar infolded epithelium and scanty colloid. Lung and spleen show chronic passive congestion. Thymus is hyperplastic.

T. C. L. A. No. 6403. S. No. 52185. W. M. *Aet.* 34. Admitted November 6, 1920. Died, November 15, 1920.

F.H. Negative.

P.H. Negative.

P.I. Well until six months ago, since then weakness, nervousness, palpitation, headache and tremor of hands. Three months ago, small swelling of neck, progressive increase. Dyspnoea now.

P.E. P. 108. T. 99. R. 24. B.P. 140/70. Undernourished, restless, siallorhoea, moderate bilateral struma—firm not nodular, with systolic thrills and bruits. Marked exophthalmos and all classical eye-signs. Brown pigmentation of skin. Lungs negative. Heart not enlarged. Systolic murmur down sternum. Rate 120, regular. No oedema. Tremor of hands. X-Ray of chest, negative. Urine negative. Electrocardiogram, Sinus tachycardia. B.M.R. plus 115.5 Operation, November 15, 1920. Ligation of both inferior thyroid vessels. Condition poor during operation. Died two hours later. Respiration became shallow and difficult. Pulse 150–200.

Impression. Exophthalmic goitre.

Autopsy. 10 hours post mortem. The heart weighs 350 gm. The right auricle is dilated. The wall of the left ventricle measures 15 mm. and in it fine scars are visible to the naked eye. The coronary vessels show very slight sclerosis. Microscopically, the right auricle shows intermuscular and perivascular fibrosis with mononuclear infiltration. In the right ventricle the change is the same but predominates around the vessels. The wall of the left auricle is without definite change and in the left ventricle can be seen only slight increase of perivascular connective tissue. The brown atrophy granules are not increased. Fat stains show no fat apart from lipochrome granules. In the thyroid the acini have small

lumina or are completely solid. Only a few contain a little thin secretion. The epithelium is columnar and shows marked papillary ingrowth. Lymphoid nodules are frequent. Lungs, kidneys and spleen show chronic passive congestion.

M. M. A. No. 6600. S. No. 53786. F. W. *Aet.* 14. Admitted June 13, 1921. Died June 13, 1921.

F.H. Negative.

P.H. Negative.

P.I. Sudden onset six weeks ago. Nervousness, vomiting—persistent. Pulse 138–152. No fever. Swelling in neck and oedema of ankles appeared. In bed for five weeks. Oedema of extremities when admitted. Died—1.45 P.M. R. 36. T. 98.6 P. 140 (weak and variable). Delirious.

Impression. Exophthalmic goitre.

Autopsy. 1¾ hours post mortem. Heart weighs 230 gm. Right ventricle measures 5 mm., the left 15 mm. No dilatation. The coronaries are normal. Microscopically, there is one small area of intermuscular monuclear infiltration. No scarring or other abnormality present. Most of the acini of the thyroid are small or solid without any colloid and with a columnar infolded epithelium. Lymphoid nodules are frequent. The liver shows periportal fat accumulation. The thymus is hyperplastic.

E. W. A. No. 7076. M. No. 47799. F. C. *Aet.* 43. Admitted June 12, 1922. Died July 23, 1922.

F.H. Non-contributory.

P.H. Frequent tonsillitis. "Inflammatory Rheumatism" at 31—in bed 6 weeks.

P.I. Increasing struma, protrusion of eyes, nervousness and loss of weight (10 lbs.) for 8 months. Cough and orthopnoea, 2 months. Swelling of legs and abdomen for one month. Diarrhoea, 4 to 5 times daily.

P.E. Small, undernourished, very nervous and apprehensive, marked orthopnoea. Skin moist and cyanotic, classical eye-signs. Thyroid diffusely enlarged, not nodular. No thrill nor bruit. R.M.D. increased. Râles at both lung bases. Heart: R.C.D. 14.5 cm., presystolic gallop, apical systolic murmur, normal rhythm, pulse rate 130 +. Ascites; liver 6 cm. below costal margin. Oedema of sacrum and ankles. Wassermann positive. Urine: Albumin 2 + to 3+, otherwise negative. X-Ray of chest: Enlarged heart and aorta. Pleurisy right base, broncho-pneumonia. Electrocardiogram: Normal sinus rhythm. Psychic disturbances set in. On July 23rd, while in a tepid pack and with pulse at 128, she died suddenly. T. (rectal) at moment of death 100°F. Temperature of pack 40°C.

Impression. Exophthalmic goitre. Myocardial insufficiency.

Autopsy. 25½ hours post mortem. Heart weighs 300 gm. Right auricle and ventricle dilated but not hypertrophied. The left chambers show some hyper-

trophy. The right ventricle measures 6 mm. and the left 18 mm. Diffuse scars are visible in the myocardium. The coronaries are normal. There is a syphilitic aortitis. In the myocardium microscopically is seen diffuse scarring around bundles of muscle fibres or even single fibres, and this loose scar contains numerous mononuclear and lymphoid cells. The perivascular fibrous tissue is not increased. Many muscle fibres contain large vacuoles. The change is present in all four chambers, most marked in the right auricle and least marked in the left auricle. Fat stains show no fat apart from lipochrome granules. The acini are of medium size but contain little colloid and show a ragged infolded columnar epithelium. The thymus is hyperplastic. There is chronic passive congestion of the spleen. In the aorta is a definite syphilitic aortitis.

L. C. A. No. 7554. S. 59837. F. C. *Aet.* 39. Admitted June 22, 1923. Died June 27, 1923.

F.H. Negative.

P.H. Negative.

P.I. Hands and feet swollen in early morning ever since childhood. This disappeared on moving about. No cardiac symptoms. Enlargement of neck since childhood. One year ago neck became more prominent, loss of weight from 160 to 120 lbs.; nervous, irritable, palpitation, appetite voracious, dyspnoeic lately.

P.E. P. 100 (Digitalis?) T. 99. R. 20. B.P. 148/78. Undernourished; asymmetric enlargement of thyroid; irregular, rubbery consistence, not nodular; voice husky. No exophthalmos or eye signs. Slight fine tremor. Lungs negative. M.L.D. 11 cm. M.R.D. 3.5 cm. C.V. Sounds forceful, regular. Systolic murmur. No arteriosclerosis. Wassermann negative. X-Ray: heart enlarged, especially to the left. Urine negative. June 25, 1923, Double partial lobectomy. Condition good but developed psychosis, very restless. Died suddenly 10.25 P.M. June 27, 1923.

Impression. Adenoma with hyperthyroidism. Post-operative psychosis.

Autopsy. 18 hours post mortem. The heart is enlarged and weighs 440 gm. The right ventricle measures 5 mm. the left 20 mm. Small scars are present in the myocardium. Microscopically, there is slight perivascular and even less intermuscular scarring. The muscle fibres are atrophic. There is some mononuclear and lymphoid infiltration beneath the epi- and endocardium especially the latter. The change is most marked toward the tip of the ventricle. The thyroid shows some acini with normal colloid content. Others small with columnar epithelium. Lymphoid accumulations are frequent in the stroma. The liver shows some central atrophy and a diffuse fatty change. There is a little early lobular pneumonia. The hypophysis is definitely atrophic.

C. S. A. No. 8233. S. No. 63580. M. W. *Aet.* 54. Admitted September 4, 1924. Died September 19, 1924.

F.H. Negative.

P.H. Negative.

P.I. Eight months ago sinus infection followed by coma, convulsions, visual disturbances and finally by eye infection. Since then quite nervous; tremor, loss of weight and strength; sweating.

P.E. T. 99. P. 120. B.P. 145/80. Emaciated, skin moist and high colour, brown pigmentation, fine and coarse tremor of hands. Eyes: doubtful exophthalmos, cellulitis of left orbit. No eye signs. Thyroid symmetrically enlarged, fairly firm, systolic bruit both sides. Heart: M.L.D. 10 cm. M.R.D. 3 cm. Moderate sclerosis of radials. Systolic shock and murmur; extrasystoles. Abdomen: negative. Urine: Albumin 1 plus. B.M.R. plus 60. Wassermann negative. Temporary improvement under Lugol's but became restless and maniacal. Pulse 160. Eyes improved. Died September 19, 1924, "with symptoms of acute cardiac failure."

Impression. Exophthalmic goitre. ?Brain abscess.

Autopsy. 3 hours post mortem. The heart is enlarged and weighs 400 gm. Apart from slight perivascular fibrosis no change is seen microscopically. The thyroid contains colloid, but the acini are small and lined with irregular columnar cells. There are bilateral corneal ulcers, one of which has perforated. The adrenals show small accumulations of mononuclear cells in the medulla. There is a cyst of the liver and the section shows also periportal lymphocytic infiltration, heripheral fat accumulation and central atrophy of the lobule. There are old miliary tubercles in the kidney. Lungs show slight lobular pneumonia.

D. J. A. No. 8103. M. No. 51337. W. F. *Aet.* 60. Admitted June 16, 1924. Died June 21, 1924.

F.H. Negative.

P.H. "Rheumatic fever" three years ago. Frequent sore throats and tonsillitis. Shortness of breath on slight exertion, 5 to 6 years. Vomiting spells of several weeks' duration for 15 years.

P.I. Below par for one year, vomiting worse, shaky and nervous, dyspnoea worse, also oedema of ankles, appetite good, always warm, emotional, very weak.

P.E. T. 99.6. P. 110. R. 24. B.P. 195/0 (several determinations). Rather obese, quiet and feeble with striking asthenia and prostration, slight dyspnoea. Skin loose and moist, cutaneous oedema everywhere. No exophthalmos nor eye signs. Thyroid moderately enlarged, soft, symmetrical systolic bruits and thrills. Lungs negative. Heart: M.D.L. 11.5 cm. M.R.D. 6 cm. X-Ray: Heart slightly enlarged. First sound loud and snapping. Pulse collapsing but regular. Abdomen negative. Coarse tremor of fingers. Marked pitting oedema over shins. W.B.C. 5,900. Mentally confused. Urine, trace albumin. Fever and pulse gradually went up. Death, June 21, 1924. T. 108. P. 150 +.

Impression. Hyperthyroidism.

Autopsy. 7½ hours post mortem. Heart weighs 540 gm. (Deceased was a very heavily built woman). Right ventricle 3 mm. Left ventricle 14 mm. Slight coronary sclerosis. Microscopically, there are areas in which muscle fibres are atrophic and surrounded by loose connective tissue, and a few mononuclear and lymphoid cells. In the thyroid the acini are small, with little colloid. The epithelium is columnar and infolded. Lymphoid accumulations are plentiful. The adrenals are small, weighing together 8 gm. The liver shows chronic passive congestion with central atrophy. The spleen contains much haemosiderin. There are hyaline tubercles in the mediastinal nodes.

S. E. A. A. No. 8145. S. No. 63069. F. W. *Aet.* 54. Admitted July 22, 1924. Died July 23, 1924.

F.H. One son has goitre.

P.H. Negative.

P.I. Neck slightly enlarged for 15 years. Six months ago began to feel weak, nervous. Aggravated 2 months ago—neck larger, palpitation, emotional instability, sweating, loss of 20 lbs. weight, dyspnoea on exertion. Moderate swelling of ankles and hacking cough.

P.E. T. 99.4 P. 116. R. 28. B.P. 135/50. Nervous, apprenhensive, has lost weight. Slight exophthalmos. Nodular asymmetrical swelling of thyroid, neck veins full. Slight lid-lag. Systolic bruit, no thrill. C.V. Systolic shock at apex. M.L.D. 9 cm. Teleo—M.R. 2.5. M.L. 8.0. Systolic murmur. Rhythm regular. Lungs and abdomen negative. Slight oedema of ankles. Wassermann negative. W.B.C. 9200. Electrocardiogram: Sinus tachycardia. Urine, Albumin 1 plus. Pulse rose rapidly, she became disoriented. Died July 23, 1924.

Impression. Toxic adenoma of thyroid.

Autopsy. Heart weighs 330 gm. and is distinctly enlarged. Fibrous scars visible in the myocardium particularly at apex of left ventricle and the base of the papillary muscles. Microscopically, the scarring is obvious, especially under the endocardium and in the papillary muscles. These areas are largely intermuscular and in them the muscle fibres become frayed out and disappear. A moderate increase of perivascular connective tissue is seen. There are scattered monocytes in the scarred areas. The thyroid contains a moderate amount of colloid but the acinar epithelium is columnar and shows marked papillary ingrowth. The adrenals are large and together weigh 30 gm. The liver shows chronic passive congestion and central atrophy. There is a slight aspiration pneumonia.

M. E. H. A. No. 8808. M. No. 53540. C. F. *Aet.* 61. Admitted August 10, 1925. Died, August 20, 1925.

F.H. Negative.

P.H. Negative.

P.I. Goitre since first pregnancy at 14. No symptoms till four years ago;

since then has had shortness of breath on exertion. Four months ago dyspnoea increased, weakness, pounding in chest. Forced to bed; cough ever since. Fluid drawn from left chest twice. Marked loss of weight in last four months.

P.E. T. 99. P. 80. R. 20. B.P. 180/62. Very emaciated, orthopnoeic, eyes normally prominent, no eye signs, a little nervous and tremulous. Globular firm swelling of thyroid in mid-line, semifluctuant. Lungs: Fluid in both sides. *C.V.* P.M.I. heaving and marked in 5th interspace 11 cm. from M.L. M.D.L. 14 cm. M.D.R. 7 cm. Marked throbbing in peripheral vessels which are markedly sclerosed. Auricular fibrillation. Systolic murmur at apex, and base. Abdomen: Liver moderately enlarged. Legs: oedematous. Electrocardiogram: Auricular fibrillation. Wassermann negative. Urine: Albumin, otherwise negative. X-Ray: Enlarged heart, dilated aorta, bilateral pleural effusion. W.B.C. 4,200. Course rapidly down-hill despite treatment. Died August 20, 1925.

Impression. Adenoma of thyroid. Hyperthyroidism. Auricular fibrillation. Arteriosclerosis and hypertension. Myocardial insufficiency.

Autopsy. 3 hours post mortem. The heart weighs 420 gm. The wall of the right ventricle measures 5 mm. that of the left 20 mm. In the left ventricle there is moderate perivascular and intermuscular scarring. Fibres in the left auricle wall contain fat. Right auricle and ventricle show no change. The thyroid is adenomatous. The nodules show acini containing colloid, but in the rest of the gland the acini are small with columnar cells and very little colloid. There are a few accumulations of lymphoid cells. The liver shows marked chronic passive congestion with central atrophy and scarring. There are gall-stones present. The thymus and other lymphoid tissues are hyperplastic. The pancreas shows some scarring and lymphoid infiltration. In the spleen the smaller arteries show in some an obliterative endarteritis; in others a hyaline change of the walls.

A. H. A. No. 8931. U. No. 568. F. C. *Aet.* 35. Admitted November 5, 1925. Died November 11, 1925.

F.H. Negative.

P.H. Negative.

P.I. Slight dyspnoea on exertion for several years. Lump appeared in neck ten years ago with nervousness and tremor of hands. Tachycardia for six years. Exophthalmos, two years. Oedema of ankles. Hot flushes. Weakness for one year. Lately nausea and vomiting.

P.E. T. 100. P. 126. R. 32. B.P. 125/65. W.B.C. 7,800. Extreme emaciation, nervousness, marked exophthalmos, purulent conjunctivitis. All hyperthyroid eye-signs. Large symmetrical enlargement of thyroid with nodule in right lobe. Pulsation marked. No thrill. No bruit. Lungs negative. C.V.: Auricular fibrillation (Ekg.) No thickening of radials, retrosternal dulness +, impulse rapid and vibratory. M.L.D. 9.5 cm. M.R.D. 4 cm. Systolic murmur at apex. Abdomen negative. Tremor of fingers. Slight oedema of shins. Urine: Trace of albumin. Rapidly went down hill in thyroid storm. Pulse 200. T. 106, more and more restless. Died November 11, 1925.

Impression. Hyperthyroidism. Exophthalmic goitre with thyroid crisis. Auricular fibrillation. Purulent conjunctivitis.

Autopsy. 9 hours post mortem. Heart not enlarged. The pericardium is adherent. In the right auricular appendage there is a thrombus. On the mitral valve and at the angles of attachment of the aortic cusps are small warty vegetations. The myocardium is very brown and throughout, especially at the base of the left ventricle, can be seen minute yellow grey flecks. Microscopically, the changes are those of acute rheumatism. There is a chronic pericarditis. There are several scars and fresh Aschoff bodies in the neighborhood of the vessels. In places are areas of necrotic muscle fibres with lymphocytic infiltration. Other fibres are hyaline and glassy. Mitral valve is thickened and vascular and shows old organized and fresher vegetations. The endocardium of the left auricle is thickened and hyaline with small foci of lymphocytes. The thyroid is adenomatous. In the nodules many of the acini are distended with colloid. In the rest of the gland, however, the majority are small with scanty thin secretion and columnar lining cells. There are some areas of haemorrhage. Liver and spleen show chronic passive congestion. There is moderate hyperplasia of the thymus. In the lung are patches of lobular pneumonia.

J. J. L. A. No. 9367. Unit No. 4589. W. M. *Aet.* 57. Admitted May 5, 1926. Died July 22, 1926.

F. H. Negative.

P. H. Negative.

P. I. Partial stroke one year ago; in bed for several months during which he lost weight—200 to 118 lbs. Three months ago neck began to swell, dyspnoea, change of voice, insomnia, tremor. Several recurrences and relapses. Fluid taken from right chest two weeks ago.

P. E. T. 99.6°F. P. 100. R. 20. B.P. 160/80. Nervous, piping voice, emotional; skin pink and moist, slight cyanosis, widened eye-slits, thyroid enlarged, asymmetric, hard nodules, no thrills or bruits. Lungs: Friction rub right front. Heart: M.D.L. 13 cm. M.D.R. 4 cm. Impulse forceful, totally irregular, systolic murmur at apex. Liver two fingers down. Urine negative. Wassermann negative. Teleo: M.R. 7, M.L. 11.5. Electrocardiogram: Auricular fibrillation. B.M.R. plus 47, dropped to plus 7 with Lugol's and then up again to plus 30. Operation: Double partial lobectomy July 21, 1926. Pulse and temperature increased a few hours later, cyanosis set in and patient died July 22nd. P. 120 (fibrillating, digitalis). T. 104.

Impression. Exophthalmic goitre. Hyperthyroidism. Hypertension. Pleurisy? (rt.)

Autopsy. 3 hours post mortem. The heart is enlarged and weighs 430 gm. The right ventricle measures 7 mm. and the left 30 mm. Microscopically, there is everywhere a diffuse destruction and disappearance of muscle fibres with areas of necrotic fibres. In other areas they are hyaline. Between these can be seen

collapsed stroma and newly formed connective tissue with a marked infiltration of mononuclear and lymphoid cells. There is a little interacinar scarring in the thyroid. Most of the acini appear normal, only a few are small with columnar epithelium. The thymus is hyperplastic. There is a general arteriosclerosis but the coronary vessels are not affected. The adrenals are enlarged but not abnormal on section. In the lung is some fresh lobular pneumonia.

E. J. A. No. 9333. Unit No. 5804. F. C. *Aet.* 56. Admitted June 25, 1926. Died June 26, 1926.

F.H. Negative.

P.H. Negative.

P.I. For two years progressive nervousness, irritability, loss of weight, dyspnoea, palpitation, goitre and exophthalmos. Vomiting after meals for two months. Fell and broke her leg last night.

P.E. T. 99. P. 125. R. 28. Restless, irrational, emaciated. Marked exophthalmos with lid-lag and corneal ulcers. Symmetrical enlargement of thyroid, diffuse soft systolic bruit, no thrill. Heart: Definite systolic shock. No murmurs. Rhythm regular. Abdomen negative. Lungs: few râles at left base. Marked tremor. Intertrochanteric fracture of left femur. No oedema. Urine negative. Pulse 180. T. 105. Moribund. Death, June 26th.

Impression. Exophthalmic goiter. Fracture of femur.

Autopsy. 18 hours post mortem. Heart weighs 300 gm. and is moderately enlarged in comparison to the size of the body. Microscopically, there is slight perivascular and even less intermuscular fibrosis, with a few scattered mononuclear cells, some lymphocytes and few polymorphonuclears and eosinophils. The fibres themselves are normal. The thyroid shows slight interacinar scarring and lymphoid accumulation. There are also occasional tubercles. Most of the acini are colloid-containing with cubical epithelium. The thymus is hyperplastic. There are tubercles and areas of caseation in the mediastinal nodes. The kidney shows chronic glomerular nephritis. In the liver there is some accumulation of cells round the portal systems; there are also a few tubercles.

N. C. A. No. 9471. Unit No. 55677. C. F. *Aet.* 35. Admitted September 22, 1926. Died September 22, 1926.

F.H. Negative.

P.H. Struma with no change in size for 18 years.

P.I. Slight shortness of breath commencing seven months ago. Eyes noticed to be more prominent. Occasionally complained of palpitation. Prepared breakfast for husband this morning and seemed all right; he returned at 7 P.M. to find her in collapse—friends say that she was that way all day. Sudden onset.

P.E. P. 140. Apex rate 240. T 101. R. 60. Extremely emaciated, restless, thrashing about, marked exophthalmos. Lids fail to close, firm smooth enlargement of thyroid. Lungs filled with râles. C.V.: Apex beating violently in sixth

interspace in anterior axillary line. Systolic murmur. Auricular fibrillation, with pulse deficit of 100. Liver down to umbilicus. Pitting oedema of legs. Died in three hours. Pulse became imperceptible two minutes before respirations ceased.

Impression. Hyperthyroidism. Exophthalmic goitre. Auricular fibrillation. Myocardial failure.

Autopsy. 32 hours post mortem. The heart is enlarged and weighs 390 gm. The right ventricle is dilated and hypertrophied, the left ventricle slightly hypertrophied. Microscopically, there is definite perivascular and rather slighter intermuscular scarring especially toward the tip of the left ventricle. There is no cell infiltration. The thyroid is adenomatous. The acini throughout appear normal, are colloid-containing and lined with cubical cells. There are some lymphoid nodules. The thymus is hyperplastic. Lung, spleen and liver show chronic passive congestion. This is marked in the liver where there is central atrophy and necrosis.

J. A. B. A. No. 1015.[3] Unit No. 15061. M. W. *Aet.* 49. Admitted November 1, 1927. Died November 26, 1927.

F.H. Negative.

P.H. Negative.

P.I. Increasing loss of strength and fatigue for 15 months. Swelling of neck appeared one year ago followed by nervousness, protrusion of eyes, loss of weight (35 lbs.) and swelling of legs and ankles. Swelling of abdomen in past two months associated with dyspnoea.

P.E. Poorly nourished, dyspnoeic, apprehensive; skin moist and warm. Well marked exophthalmos with classical eye-signs. Marked struma, uniformly and smoothly enlarged, bruit well heard. Râles at both lung bases. Heart: M.L.D. 16 cm.; M.R.D. 4.5 cm.; rhythm totally irregular with pulse deficit of 12 per minute. Systolic murmur at apex. B.P. 136–124/86–72. Liver edge 6 cm. below costal margin. Ascites present. B.M.R. plus 35 to plus 51. Urine negative. Prepared for operation with Lugol's and digitalis. Double partial lobectomy on November 23rd, 1927. Pathological report: Exophthalmic goitre. 11/26/27, seemed to be improving. Complained of pain over heart and left shoulder, pulse slowed to 70–80 per minute and he died suddenly 15 minutes after, complaining of pain. Respirations and pulse ceased at same time.

Impression. Exophthalmic goitre. Myocardial insufficiency. Auricular fibrillation.

Autopsy. 10 hours post mortem. The heart is distinctly enlarged, weighs 400 gm. The muscle is soft and flabby. The right ventricle measures 4 mm. and the left 14 mm. Both are dilated as well as hypertrophied. A few fine scars are apparent in the myocardium of the left ventricle. The coronaries show slight

[3] This case has been reported in detail by Dr. Henry M. Thomas (3).

sclerosis but no encroachment on the lumen. There is a thrombus in one of the smaller coronary branches. The section shows slight increase in connective tissue around a few vessels, a few mononuclear and lymphoid cells and in one area some polymorphonuclears. A frozen section shows no fat. The thyroid shows normal colloid-containing acini. There are a few lymphoid nodules. There are several infarcts in the kidney. The thymus is hyperplastic. The lungs show chronic passive congestion and edema. There is a portal cirrhosis of the liver and some chronic passive congestion.

E. H. A. No. 10344. U. No. 16297. C. F. *Aet.* 46. Admitted January 15, 1928. Died April 19, 1928.

F.H. One sister had heart trouble for fifteen years.

P.H. Doubtful rheumatic fever at 30.

P.I. Onset five months ago with palpitation, precordial pain, exophthalmos. Loss of weight (120 to 80 lbs.) and nervousness, dyspnoea, weakness, sweating. Progressive. Polyphagia, swelling of feet, marked tremor. Two weeks ago swelling in neck noted. Three weeks ago sudden increase of all symptoms.

P.E. T. 98.9. P. 120. R. 32. B.P. 170/80. Emaciated, restless and overactive; pigmentation, sweating, eyes staring, poor convergence. Diffuse soft symmetrical enlargement of thyroid, pulsations but no thrills or bruits. Lungs negative. C.V.: Apex beat in 5th, 9 cm. from M.L. M.D.R. 3 cm. Systolic murmur at apex. Impulse marked. Rate and rhythm regular. No oedema. Wassermann negative. Urine negative. B.M.R. varied from plus 125 before iodine therapy to plus 40 after it. Despite heroic treatment she became more toxic, developed an unknown infection and died April 19, 1928.

Impression. Exophthalmic goitre. Thyroid crisis.

Autopsy. 24 hours after death. The heart weighs 280 gm. The right ventricle is dilated, the left slightly hypertrophied. There are a few small subendocardial haemorrhages. The right ventricle measures 4 mm. and the left 16 mm. Microscopically, there is some perivascular fibrosis and very slight intermuscular scarring with a few mononuclear cells. The change is most marked in the right auricle and left ventricle. No fat seen apart from lipochrome granules. In the thyroid the acini for the most part appear normal. The adrenals are large and together weigh 20 gm. The thymus is hyperplastic. Spleen and liver show chronic passive congestion and the latter shows some periportal accumulation of lymphoid cells. There are some areas of aspiration pneumonia and a slight cystitis.

M. R. A. No. 11175. U. No. 27240. F. W. *Aet.* 63. Admitted October 3, 1929. Died October 31, 1929.

F.H. Negative.

P.H. Malaria at 11 years. Pneumonia at 16. Palpitation for several years. Period of depression in 1927.

P.I. Onset in 1925 with increased nervousness. Tremor, palpitation, anorexia and some dyspnoea. In 1927 mental depression. Lost 50 lbs. After a rest of 6

months, largely recovered, regained her weight. In November 1928 her symptoms underwent an acute exacerbation and by March 1929 she had lost 90 lbs. of weight. Nausea and vomiting appeared. After hospitalization she improved somewhat and regained 40 lbs. In April 1929, neck began to swell and was told that she had a goitre. For past four or five years moderate dyspnoea on exertion. No orthopnoea.

P.E. T. 99.6. P. 84. R. 20. B.P. 146/66. Considerable loss of weight. Alopecia and leucoderma. Von Graefe's and Stellwag's signs, slight exophthalmos. Enlarged nodular thyroid—thrill—bruit—, extends substernally probably. Increased R.M.D. Tremor of outstretched fingers. Moderate dullness, some diminution of B.S. and tactile fremitus over left lower chest posteriorly. Peripheral sclerosis. Slight sclerosis of retinal arteries. Wassermann negative. B.M.R. plus 71. 10/31/29. Double partial lobectomy. Followed immediately by a terrific post-operative reaction. Died 48 hours after operation. Fever rose to 107°F.; W.B.C. rose to 17,600.

Impression. Exophthalmic goitre.

Autopsy. 1½ hours post mortem. The heart weighs 370 gm. and appears normal. Microscopically, there is no abnormality save very slight perivascular and intermuscular fibrosis. In the thyroid most of the acini are normal but some are small, without colloid and with columnar lining cells. There are small abscesses in the liver. There is slight atheroma of the aorta. In the medulla of the adrenal are a few lymphoid cells. The lung shows lobular pneumonia.

E. K. A. No. 11483. U. 31101 W. F. *Aet.* 36. Admitted May 14, 1930. Died June 4, 1930.

F.H. Family tendency to obesity on both sides.

P.H. Told 15 years ago she had kidney trouble.

P.I. Gradual enlargement of neck during past 5 years. No constitutional symptoms until 2 months ago; since then increasing nervousness. Has lost weight rapidly (12 lbs.), become very nervous and has had smothering sensations. Short of breath, sweats profusely.

P.E. T. 99.2° P. 120. R. 26. Pale, nervous, emotional; considerable brownish pigmentation. Eyes prominent, slight lid-lag. Thyroid moderately and diffusely enlarged. No thrill nor bruit. No nodules. Heart slightly enlarged. B.P. 180/100. M.R. 4.5 cm. M.L. 8.4 cm. T. 25.5. Action forceful; soft systolic murmur over entire precordium. Lungs negative. Abdomen negative. Minimal pitting oedema of ankles. B.M.R. plus 36. B. Wassermann negative. Blood N.P.N. 72 per cent mg. Urine negative. Electrocardiogram: Normal sinus rhythm. Following a course of Lugol's solution (3 cc. q.d.) B.M.R. fell to plus 19 in 14 days. Subtotal thyroidectomy was performed June 2nd, following which pulse and temperature rose rapidly and she died apparently a toxic death. Uraemia (?)

Impression. Nodular goitre with hyperthyroidism.

Autopsy. Heart weighs 390 gm. Slightly enlarged. Myocardium paler than normal. Auricles dilated. No coronary sclerosis. Microscopic: Little thickening of endocardium. Small area of fragmentation of fibres, otherwise normal. B.A. granules +. Thyroid adenomatous. Most acini contain colloid, and the cells are flat or cubical, few acini hyperplastic. Much scarring and numerous lymphoid nodules. Thymus moderately hyperplastic. Kidneys: Chronic nephritis.

H. T. A. No. 11604. U. 31771. F. W. *Aet.* 33. Admitted June 22, 1930. Died August 29, 1930.

P.H. Negative.

F.H. Negative.

P.I. Eleven months ago sudden appearance of swelling of neck, nervousness, emotional lability. Has lost 15–20 lbs. in weight. Marked palpitation.

P.E. T. 99°, P. 110, R. 22. Undernourished, restless, skin moist. Marked exophthalmos with classical eye-signs. Very large lobulated thyroid gland which pulsates and over which there is a thrill and bruit. Some tracheal obstruction. Lungs negative. Heart: B.P. 125/70. Moderate enlargement. M.L.D. 13.0 cm. Marked pulsation. Loud systolic murmur over precordium. Abdomen negative. No oedema. B.M.R. plus 58. Blood Wassermann 4 plus. Urine negative. With rest and Lugol's solution she gained 15 lbs., but the pulse and B.M.R. remained high. Subtotal thyroidectomy, following which she became rapidly worse and died suddenly 2 hours later.

Impression. Exophthalmic goitre.

Autopsy. Heart weighs 400 gm. Small subepicardial haemorrhages. Myocardium pale and soft. Coronaries tortuous but not sclerosed. Right ventricle 0.6 cm. Left ventricle 1.7 cm. Fine intermuscular scars. Increase of perivascular fibrous tissue. Microscopic: Some areas of hyaline and necrotic fibres. Few mononuclear cells. B.A. granules—. Thyroid shows no adenomata. The acini contain colloid but have irregular high epithelium. There is an acute splenic tumor. Liver shows marked periportal and lymphoid infiltration. Thymus is hyperplastic. Intestines shows lymphoid hyperplasia.

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CERTAIN ASPECTS OF SYPHILITIC CARDIAC DISEASE[1,2]

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Considered in its broadest aspects cardio-vascular syphilis offers a unique field of study to those historically minded as well as to those of us who, primarily as clinicians, have to do with the care of patients, the subjects of this destructive and insidious malady.

Unlike the lesions of arteriosclerosis which are so generally encountered in the later years of life, the brunt of the attack in syphilitic aortic disease is advanced upon those in the early and middle decades in the very prime of life. In this respect it differs also from the prevalent tendency of rheumatic disease which strikes, often so ruthlessly, in the early years.

Against the late effects of the infection with the spirochaeta pallida, often so tragically portrayed, it may be said, we think without contradiction, that we have at least made some headway in mitigating the subjective distress, all too common an accompaniment of its evolution. But we are still unfortunately a long way from the desired goal in controlling its prevalence and in staying its slow progress. Of all the infections to which man is subject syphilis stands out as biologically far and away the most important, if for no other reason than that of its hereditary transmission. Osler (20) used to delight in saying to his students: "Study one disease, study syphilis thoroughly and you take a knowledge of all the others on the way—general medicine, nearly all surgery and certainly all the specialties."

HISTORICAL

It is of historical interest that the first accurate knowledge of the part played by, and the pathology of, syphilitic involvement of the aorta, is at most but little more than fifty years old. The frequent

[1] Delivered as a Friday afternoon lecture before the New York Academy of Medicine, January 30, 1931, by E. P. C.

[2] Submitted for publication March 2, 1931.

occurrence of aneurysm in individuals the subjects of syphilitic disease was, it is true, recognised many years ago. There is an impression conveyed by certain writers that Ambroise Paré (24) (1510–90) was the first to emphasise the frequent occurrence of aneurysms in the presence of syphilis. In a careful search through Paré's chief writings we have been unable to satisfy ourselves that this is a wholly justifiable impression. There can, however, be no question as to the emphasis placed by Morgagni (18) (1682–1771) upon the association of the two conditions. He also first described cerebral gumma and was the first to describe what was clearly a case of heart block with the Stokes-Adams syndrome, though not, of course, called such.

There exists, however, a great gap between this earliest recorded emphasis of the connection between cardio-vascular disease and syphilis and the present day conception of the intimate relationship between the two: a gap which has been only gradually bridged and which contains an interesting history of the development of our knowledge based upon many important contributions to the subject. Depending upon the nationality of the writer there exists a wide difference of opinion upon the question of priority in this matter.

If we accept the point of view of the French School the earliest descriptions of definite cardiac involvement, interpreted, however, as a lesion of tertiary syphilis, must be ceded to Ricord (26) writing in 1845. It is of interest that Ricord was born in Baltimore of French parentage. He later returned to Paris and became a graduate of the Paris faculty. Considering, however, the more specific involvement of the vascular system, Heubner's (12) paper appearing in 1874 was among the earliest to recognise the specific involvement of the smaller vessels of the brain. Köster (13), in 1875, discussed in the briefest of notes the relationship of chronic mesarteritis and the development of aneurysms.

In a paper by Welch (34), appearing in 1876, nine years before Döhle's, he describes both the macroscopic and microscopic appearance of syphilitic aortitis. As pointed out by Lamb (14), it is strange that the important fact that Welch actually emphasised the causal relationship between syphilis and aortitis has been so generally overlooked. There is, it is true, no reference to Welch's paper in Döhle's contribution nine years later and it has not been given the recognition in the literature of the subject which it deserves.

To Döhle (6), writing in 1885, and again ten years later (7), is generally conceded the credit for having first made clear and insisted upon the direct causal connection between the syphilitic infection and the lesions in the aorta. Working in Heller's Pathological Institute in Kiel he had the advantages of unrivalled material and the support of Heller himself in his insistence upon the significance of the lesions found *post mortem*. Heller's papers, the earlier a short polemic refuting an implied criticism of Döhle's original contribution, and his later one, in which he comes again to the support of the work from his institute, are of importance in this connection. Hence the origin of the early nomenclature—Döhle-Hellerschen Aortitis.

Others had indeed recognised the peculiar pathological changes so often met with in cases of aneurysm in individuals the subjects of syphilis coming to necropsy, but had failed to insist with sufficient emphasis upon the essential specific nature of the aortitis.

At this time the whole question was in a state of critical discussion and a period followed during which the general interest in the subject flagged. It was not until some years later, following the meeting of the German Pathological Society in 1903, that as a result of the papers and discussion at this meeting by Chiari (4), Benda (1) and Marchand (17) it became a subject of renewed interest and study. Among the more recent contributions to the subject the paper by Longcope (16) is a most complete and thorough discussion of every phase.

Long interested in certain aspects of syphilitic cardio-vascular disease we are quite conscious of the fact that there is little that has not been told before. May we, however, emphasise certain features that seem to us of clinical significance and importance in this condition. It has been possible to undertake a study of the cases of syphilitic aortic disease, aortitis, aortic insufficiency either alone or combined with aneurysm, and of aneurysm alone, admitted to the wards of the Johns Hopkins Hospital since 1910, at which time the Wassermann test came into accepted use.

We have arbitrarily divided our available material, comprising in all a large series of cases (867), into two periods: the first from 1910 to January 1, 1918 during which time the Wassermann test was done upon suspected syphilitic cases; the second from January, 1918 to February 20, 1930, during which time the Wassermann test was carried out on all patients admitted to the public or private wards.

We have completed a detailed analysis of the first 100 cases. This has been supplemented by the pathological findings in those cases that came to necropsy. Our remarks are based chiefly upon this series, together with certain additional clinical material including the statistical figures of the remaining cases of the entire series.

DETAILED ANALYSIS OF 100 CASES

In regard to the race and sex distribution of cardio-vascular syphilis our series re-emphasises what has been recognised, and has been so

TABLE I

Incidence of syphilis (positive Wassermann) in total admissions to Medical Service, January 1, 1918 to February 20, 1930

	MEDICAL ADMISSIONS	SYPHILIS	PER CENT
Total	20,893	2,196	10.51
Total white	17,126	1,227	6.90
Total colored	3,767	969	25.72

Ratio: total white: total colored = 4.55:1

Ratio: total white syphilis: total colored syphilis = 1.26:1.

WHITE MALE		WHITE FEMALE		COLORED MALE		COLORED FEMALE	
Medical admissions	Syphilis	Medical admissions	Syphilis	Medical admissions	Syphilis	Medical admissions	Syphilis
9,350	914	7,776	313	1,825	566	1,942	403
9.77%		4.03%		31.01%		20.7%	

strikingly shown by Turner (31) in his analysis of the distribution of the disease in 10,000 ambulatory cases, that the incidence of vascular syphilis in the colored is twice and more that in the whites. Turner says that "although race seems an important factor, it is not the sole one that determines clinically recognisable cardio-vascular lesions in the course of a syphilitic infection."

However that may be, the great susceptibility of the colored race to the major infections, syphilis and tuberculosis, has long been known, and whatever the fundamental factors at work, whether physical or

moral or both combined, we have profited much by a study of the former in peculiarly favorable soil.

In this connection the incidence of syphilis in the total admissions to the wards of the Johns Hopkins Hospital Medical service from January 1, 1918 to February 20, 1930 is of interest. It is seen at once that the incidence of the disease is almost four times as great in the total colored as in the total white admissions, and is three times more frequent in the colored males than in the white males.

Equally illuminating is the relationship of syphilis of the aorta, including aortic insufficiency and aortic aneurysm, in patients with syphilis admitted to the public and private wards over the same period.

TABLE II

Incidence of syphilis of aorta (aortic insufficiency and aortic aneurysm) in patients with syphilis (positive Wassermann) admitted to Medical Service in Johns Hopkins Hospital, January 1, 1918 to February 20, 1930

	SYPHILIS	SYPHILIS OF AORTA	PER CENT
Total cases	2,196	488	22.22
Total colored male	566	246	43.46
Total colored female	403	71	17.67
Total white male	914	142	15.53
Total white female	313	29	9.27
Total male	1,480	388	26.14
Total female	716	100	13.97
Total colored	969	317	32.61
Total white	1,227	171	13.93

Here again the percentage incidence of vascular lesions in the presence of known syphilitic infection is almost three times as great in the colored male as in the white and almost twice as great in the corresponding female group, the total male incidence being practically double the total female figure. It is of interest that the incidence of involvement of the aorta in relation to the total number of cases of proven syphilis is but 22.22 per cent. (These figures refer to aortic insufficiency and aneurysm.) When, however, we analyse the figures from the standpoint of race and sex, the incidence is more than twice as great in the colored as in the white. (Figures in close agreement with Turner's series.)

From Table III illustrating the incidence of heart disease and the mortality statistics for the same period, and the comparison with the total number of cases of syphilis of the aorta, one sees at a glance the high mortality rate, more than twice that encountered in the series of non-syphilitic heart disease, 38.11 per cent as against 16.77 per cent.

We have not attempted to differentiate the cases of aortitis as such from the combined lesions. It was thought that the necessary criteria in this early series were not sufficiently accurate. With the development of a demonstrable increase in the retro-manubrial dulness in the second interspace, clinically or by x-ray, with a ringing tympanitic

TABLE III

The incidence of heart disease and the mortality statistics in cases on the Johns Hopkins Hospital Medical Service, January 1, 1918 to February 20, 1930 and a comparison with cases of syphilis of the aorta

Total admissions	20,893
Total cases of heart disease	3,223
Per cent of total admissions	15.42
Total cases of non-syphilitic heart disease	2,735
Died	458
Per cent mortality	16.77
Total cases of syphilis of aorta	488
Per cent of total admissions	2.33
Died	186
Per cent mortality	38.11
Percentage incidence of syphilis of aorta to all cases of heart disease	15.14

quality of the second aortic tone, such an early diagnosis may be assumed with a reasonable degree of accuracy when associated with the significant symptoms of precordial or substernal pain and nocturnal or paroxysmal dyspnoea. Uncomplicated syphilitic aortitis constituted 5.1 per cent (332) in Turner's series of 10,000 ambulatory patients; it is utterly improbable that in any series of ward cases the percentage incidence of early aortitis can be more than 2 or 3 per cent. This is particularly true of the public wards to which these cases are seldom admitted before the development of signs other than those of an uncomplicated aortitis.

That the exact diagnosis of an uncomplicated aortitis is always a

simple matter is open to question. In some instances the evidence is plain, but there are many cases in which it is difficult indeed to be certain of one's criteria. It is in this field that careful x-ray and fluoroscopic study may be of the greatest value.

The distribution of the lesions in this series together with the age, race, sex and occupation are shown in Table IV.

The evolution of cardio-vascular syphilis falls essentially into three groups of cases, aortitis, aortic insufficiency and aneurysm alone or

TABLE IV

Analysis of 100 cases of syphilis of aorta

Aortic insufficiency	58
Aortic insufficiency with aneurysm	18
Aneurysm of aorta	24

I. Age

20–30	30–40	40–50	50–60	60–70	70–80
8	26	38	20	7	1

II. Color and sex

Male white	35	Total male	85
Male colored	50	Total female	15
Female white	2	Total colored	63
Female colored	13	Total white	37

III. Occupations

Laborers	59	Professional men	6
Clerks	22	Housewives	13

combined, to which may be added a fourth group, in our experience few in number, in which the myocardium alone is the seat of the chief and conspicuous lesion without aortic insufficiency or any endocardial lesion, but with occasional pathological evidence of very early aortitis. It should be clearly insisted upon that this relatively early syphilitic myocardial disease does not imply or include gumma.

Every individual having a syphilitic infection is, as is well known, a potential subject of cardio-vascular disease. What constitutes the

predisposing factor which determines the peculiar arterial invasion with the ultimate involvement of the aortic ring or the development of an aneurysm is not clearly understood. The question as to why the pulmonary artery escapes a similar fate has not been satisfactorily answered. Is it solely the factor of stress and the added burden upon the aorta which turns the balance? An unique case of Ayerza's disease, chronic cyanosis, dyspnoea and erythremia, associated with syphilitic arteriosclerosis of the pulmonary artery with all the characteristics of a syphilitic mesarteritis, has been described (32). An instance of syphilitic involvement of the pulmonary artery in which spirochaetes were demonstrated has also been reported (33). Other occasional cases appear in the literature, but how rarely!

In a series of 288 necropsies Turnbull (30) has described two instances in which syphilitic arteritis was present in the main pulmonary artery and in the chief branch to the lower lobe of the right lung.

It is of interest in this connection that in Bengal, India, extensive atheroma of the pulmonary arteries without marked involvement of the systemic vessels, and without valvular disease, has been described as "A not very rare cause of fatal cardiac dropsy." These cases occur nearly always between the ages of 20 and 40 and are thought by Rogers (27) to be "almost certainly syphilitic in origin."

HISTORY

Clinically the history of the development of cardio-vascular syphilis has certain aspects common to every such case. Typically characteristic of the great majority is the story that the individual was utterly unaware of any disability up to the time when the subjective symptoms first appeared. There may be and often is, of course, the history of the initial infection and even a history of previous specific treatment, but how seldom are the symptoms of distress associated in the individual's consciousness with this possibly forgotten experience! The exclusion of any history of rheumatic fever is, when possible, of the greatest importance, as will be emphasised. It is astonishing how often the story is one of "shortness of breath on exertion and slight swelling of the feet and ankles at the end of the day" as the earliest evidence of circulatory embarrassment. The onset then may be characterised as *relatively abrupt*. Some individuals may also give

a history suggestive of rheumatic fever as a polyarthritis years before. Such a story may add confusion to the clinical interpretation of the signs suggesting mitral disease in the presence of aortic insufficiency; certain points of significance in the differentiation are emphasised later. We have been surprised that a history of polyarthritis occurs in 11 (10 per cent) of our series. It is a clinical impression that the occurrence of the two conditions in the same individual is not at all common. Pathological evidence of rheumatic disease was present in but 3.33 per cent of our cases coming to necropsy.

THE WASSERMANN REACTION

In an extremely high percentage of cases there is a positive Wassermann reaction, not a single such determination but two or more positive findings. Excluding three cases in which no record of any Wassermann reaction appeared, there was a positive reaction in 90 of the 97 cases, or 92.6 per cent, a figure in excess even of many published statistics. Whether this unusually high incidence will be maintained in the subsequent series is uncertain.

Latent period

Our figures for the characteristic latent period from the date of the primary lesion to the first appearance of subjective symptoms are very like many such published statistics, the two extremes being three years, with fresh lesions found at necropsy, and thirty-nine years, the average duration being fifteen years and five months. One gathers the impression from clinical experience, and perhaps from slight evidence in the literature, that those individuals with the shorter latent period really represent a greater susceptibility to the infection, or that it is not, at least entirely, within the province of therapeutic control.

In rare instances the infection develops with remarkable rapidity, symptoms having appeared within seven months of the initial lesion (15). Brooks has even reported two cases of aneurysm with death within six months of the primary infection (3).

Early in the progress of the disease, among the many subjective signs of distress, weakness, giddiness, fainting, smothering sensations, "misery" in the chest and cough are frequently noted—that great

group of conscious discomforts which may mean so little or again so much. When to this congerie of complaints is added the definite statement of *shortness of breath* or *pain* or both, with early puffiness of the feet and ankles, they acquire at once an entirely new significance.

Dyspnoea and pain, each in its own peculiar fashion, constitute the two most important symptoms. Dyspnoea, as is to be expected, is more often met with in the group of aortic insufficiency alone or combined with aneurysm, 44 of 76 such cases (58 per cent), while pain about the heart was noted in but 19 (25 per cent) and significant oedema of the legs in 15 (19.73 per cent).

By contrast, in the aneurysmal group pain was present in some form in 20 (83.33 per cent) while shortness of breath occurred in only 7 of the 24 cases (28.75 per cent). It is of course recognised that this difference depends upon the location of the aneurysm.

Exertional dyspnoea, oedema, cough, pain in the chest, palpitation, smothering sensations, haemoptysis, ascites, syncope and still other manifestations may one and all occur as the symptoms of cardiovascular disease other than syphilitic involvement of the aorta. When, however, the dyspnoea or the pain occurs in *paroxysmal* attacks, either one acquires a unique and typically characteristic meaning. Although it is true that the attacks of paroxysmal dyspnoea may occur at any time, they are prone to appear at night and in this feature they assume an added diagnostic significance. Ushered in abruptly, often in the stormiest fashion, even waking the individual from sleep, lasting a few minutes to fifteen or twenty or longer, with intense air hunger and at times characterised by great expiratory distress, they may constitute an appalling clinical picture. Finally, subsiding fairly rapidly, the attack passes off leaving the individual in a state of sheer exhaustion. Even when less severe, there is the same abrupt onset. In some instances pain is an accompaniment of these attacks—typical paroxysmal dyspnoea occurred in 25 (32.90 per cent) and nocturnal dyspnoea in 35 (46.05 per cent) of the aortic cases, and in but 4 (16.66 per cent) and 3 (12.50 per cent) of the aneurysms. This is a greater incidence than is given in some of the reported series. It is true that these figures include a fairly large percentage of negroes. Paullin (25) in his discussion of syphilitic infection in the negro does not give comparable figures covering this point.

May we emphasise again that the *paroxysmal dyspnoea* of syphilitic aortic disease is signalised by typically characteristic features which serve to differentiate it from the attacks of dyspnoea met with under other conditions so often associated with advanced arteriosclerosis and grave myocardial damage from other causes. It is interesting that in rheumatic infections, which we know may involve the aorta in a way very similar to syphilis, the incidence of attacks of cardiac dyspnoea is at most extremely small. We can not recall having seen such paroxysmal dyspnoea in rheumatic disease. In a series of 768 cases reported by White and Palmer the incidence is 2.2 per cent.

In this connection we wish to emphasise how difficult it is in the matter of our terminology to break away from traditional usage even though long known to have been loosely if not incorrectly applied. The term "cardiac asthma," an old and honored designation, is today both misleading and confusing and should give place to the simple descriptive statement of cardiac dyspnoea. As long ago as 1897 Osler (21) wrote: "the disorder was confounded with cardiac asthma which we now term cardiac dyspnoea." Others (19) have expressed the same thought in the hope that our nomenclature, difficult enough as it is, might be helped towards simplicity and exactness.

A history of pain in some form is very common. Equally "significant" are the attacks of paroxysmal pain, abrupt, often radiating, even typically anginal in character, occasionally extreme; these constitute a unique and distinctive symptom. Pain may also occur as the only symptom for months in any one of several types of subjective distress. In its paroxysmal form and in those attacks which may simulate a true angina, preceding often for months the development of an aneurysm, it is a symptom of the greatest clinical interest. Osler (22) in a delightful clinical paper long ago called attention to the significance of the anginoid pain in these cases.

Any discussion at this time of the pathological physiology of the pain in syphilitic aortitis or as an early symptom of aneurysm would take us far afield. That it must be associated with the extraordinarily rich nerve and ganglia distribution in and about the root of the aorta in the aortitis, which must also play a rôle through reflex irritative disturbances in the paroxysmal dyspnoea, is a reasonable assumption, but the mystery of the anginal attacks is even today

not wholly clear. We know the views of the two schools of thought, if we may term them such, as represented by Allbutt's writings on the one side and shall we say Mackenzie and Wenckebach on the other. In this connection Singer's (28) experimental evidence is of interest as indicative of the seat of cardiac pain in the vessel sheaths. It is difficult to conceive of all cardiac pain as due to a simple ischaemia, or to coronary disease as such, or to tiny twig thrombosis. It must be admitted, as expressed by Osler, that "true angina pectoris is an arterial incident," but how may we categorically define all the other types of pain?

Pain described as dull or intermittent, referred to the heart, occurred in 40 (52.63 per cent) of the 76 aortic insufficiency cases, and

TABLE V

Subjective symptoms

	AORTIC INSUFFICIENCY ALONE OR COMBINED WITH ANEURYSM, 76 CASES		ANEURYSMS ALONE, 24 CASES	
	Number	Per cent	Number	Per cent
Exertional dyspnoea	71	93.42	13	54.16
Paroxysmal dyspnoea	25	32.90	4	16.66
Nocturnal dyspnoea	35	46.05	3	12.50
Pain in chest	40	52.63	20	83.33
Nocturnal paroxysmal pain	13	17.10	6	25.00

nocturnal paroxysmal pain in 13 (17.10 per cent). In the aneurysmal series pain referred to the heart occurred in 20 (83.33 per cent) and nocturnal paroxysmal pain in 6 (25 per cent).

May we emphasise then the significance of these two major symptoms.

Findings of note over the precordium

We have not attempted to give the exact measurements of the retrosternal dulness at the base. In 40 to 50 per cent of the aortic group there was a clinically demonstrable increase beyond the normal limit of dulness in the second interspace.

Cardiac hypertrophy was a very constant finding in the aortic group, varying greatly in degree. In the series of aneurysms alone, on the

contrary, it is conspicuously absent. This is a well established fact and often of great help in interpreting the character of obscure dulness or shadows to the right of the cardiac border.

Alteration in the intensity and tone of the second aortic sound

In the diagnosis of early uncomplicated aortitis slight changes in the pitch and quality of the aortic closure are of the utmost importance, and in the more advanced lesions associated with aortic insufficiency and aneurysm are of even greater significance. A mere accentuation of the intensity of the aortic second tone may be, it is true, associated with pathological change of moderate extent, but is far more often an expression of altered pressure relations in the peripheral vessels, an indication of increased pressure levels. With a fairly high systolic and diastolic pressure and a high pulse pressure the accentuation of the closure of the aortic cusps may be much increased and is often palpable as a distinct diastolic impact or shock. When, however, there is a distinct change in the quality of the second aortic sound at the aortic area tending towards the ringing, bell-like tympanitic tone so familiar in these cases, it conveys but one meaning, and it is evidence of definite structural change at the aortic ring or at the very origin of the ascending arch or both. It can not be too strongly emphasised that this change in tone occurs independently of any alteration in or association with high pressure levels, though of course such increase in the blood pressure may be and often is an associated condition. The point we wish to make may be stated thus: Increased accentuation alone connotes high pressure levels; a change in the quality to the metallic tympanitic klang means structural alteration in the cusps, ring or vessel. Absence of the tympanitic bell-like second sound does not of course imply the converse of this statement.

A diminished aortic second sound, on the other hand, is frequently encountered in these cases as an accompanying bit of evidence in those instances in which the insufficiency of the aorta, or the structural damage, is such that proper closure does not occur or is masked by the diastolic murmur present. As an aid in the diagnosis of doubtful cases of aortic insufficiency Thayer has emphasised the diminished or even absent second aortic sound when auscultating over the vessels of the neck.

One other clinical hint may be referred to here as a general statement. Unusual cardiac enlargement without demonstrable cause, in the absence of valvular murmurs, with a moderately diffuse apex thrust, with a first sound at the apex that has lost its clear muscular tone, with but poor filling of the peripheral vessels and a lower systolic blood pressure than one would expect from the degree of enlargement and character of the apex impulse, with a positive Wassermann reaction, should suggest syphilitic involvement of the myocardium. Even in the absence of a positive Wassermann reaction such a possibility should not be too lightly dismissed.

The presence of the Flint murmur, apart from its clinical significance as a late sign of the progressive aortitis with aortic insufficiency, assumes an especial interest in those cases in which it is essential to exclude the existence of organic mitral disease—the sole possible evidence of a previous rheumatic infection.

A typically characteristic Flint murmur was present in 45 (59.21 per cent) of the 76 cases and in 4 was associated with a palpable thrill at the apex. It may be stated, categorically we believe, that in the presence of a conspicuous aortic insufficiency with a greatly hypertrophied left ventricle, the presence of the characteristic Flint murmur even when accompanied by a late diastolic thrill, call it presystolic if you will, does not justify the diagnosis of mitral disease except in the absence of all the criteria indicative of syphilitic disease and the presence of a definite history of rheumatic infection with possibly previous attacks of recognised rheumatic endocarditis in the past, and such clinical signs as increase in the intensity of the first sound at the apex and enlargement of the left auricle.

This distinction can not be too strongly emphasised. It has been forced upon us only after more than one humiliating lesson—in the failure of the pathologist to confirm the clinical description in such cases.

Whatever the actual explanation for the Flint murmur it may in some instances simulate the murmur of mitral stenosis in a truly remarkable manner. The whole question is discussed at length in Thayer's (29) paper, to which nothing of importance has been added in recent years.

Hermann (11) has advanced the suggestion based upon clinical

observation that the Flint murmur was associated with conspicuous involvement of the posterior cusp of the aortic valve. He has confirmed this observation experimentally in two dogs. This suggested to us the attempt to correlate the clinical record of a Flint murmur with the aortic cusp (or cusps) involved, as evidenced by the pathological description in those cases which have come to necropsy. Unfortunately, it has not been possible to establish any relationship with the presence of a Flint murmur clinically and any single aortic leaflet. In the large majority of instances the root of the aorta, the entire aortic ring and all the cusps show a similar degree of involvement, and in many cases, in addition to the changes in the leaflets, the characteristic extension of the syphilitic process with a separation of the cusps at their lateral margin of attachment is described.

Disturbances of the cardiac rhythm

One other point of clinical and diagnostic significance remains to be mentioned and that is the entire absence of auricular fibrillation in this series of 100 cases. Though we can not at this time give the exact figures for the total cases of our later series, it is our impression that auricular fibrillation will be found to occur in perhaps 3 per cent of the total. (In 574 cases of clinical auricular fibrillation syphilis of the aorta was present in but 3 per cent.) This is a most important and significant clinical fact. The absence of this, and of other irregularities generally, in syphilitic aortitis with aortic insufficiency alone or combined with aneurysm, has been commented upon by many writers and has long been well known, but we sometimes wonder if the rarity of auricular fibrillation, even though there is so slight a pathological basis for its occurrence, has been sufficiently emphasised as of clinical significance in differentiating rheumatic or arteriosclerotic disease from syphilitic in the doubtful cases one occasionally encounters. In our series of rheumatic cardiac disease auricular fibrillation has occurred either as a transient phenomenon or permanently established in over 85 per cent of the cases coming to necropsy.

Premature contractions, more often ventricular in origin, occurred in 16 of the total 100 cases. The incidence of many other symptoms and objective signs might perhaps be discussed as a part of the complete clinical picture, but as they are, at least most of them, incidental

to the course of progressive cardiac failure in general, any discussion of them at this time is omitted.

Certain features, however, which are of general interest may be alluded to before we summarise the important symptoms and signs. The absence of fever is notable in our series. The temperature did not go above 100.6° except in the presence of obvious complicating infections (16 cases). Tracheal tug (20), anisocoria (8), changes in the voice (9), clubbing of the fingers (3) and precordial tenderness (1) occurred in a scattering incidence.

We have made but slight reference to the importance of the x-ray findings and to their value in the confirmation and interpretation of the physical findings in all lesions of the cardio-vascular system. We have been concerned essentially with certain purely clinical aspects of syphilitic cardio-vascular disease; the importance of, and the invaluable help to be gained from, careful fluoroscopic study is too well known to need comment. We know that in many instances the fluoroscope is the sole source of the ultimate convincing evidence of dilatation of the arch of the aorta and aneurysm.

You may ask, How then have we arrived at the clinical criteria which would justify the interpretation of the presence of cardio-vascular syphilis? In setting up the necessary criteria for the diagnosis of aortic insufficiency or aneurysm we have established seven fundamentally important and significant data and then have assumed that, if any five of these were clinically demonstrable, the diagnosis of syphilitic aortic disease was justifiable. To these must, of course, be added the well known signs essential for the diagnosis of aortic insufficiency alone or combined with aneurysm or of aneurysm alone.

As suggested in the outline given these are as follows:

I. The history of a relatively abrupt and unexpected onset of the symptoms of circulatory embarrassment.
II. Demonstrable increase in the retromanubrial dulness in the second interspace, with change in the quality of the aortic second sound, together with fluoroscopic evidence of aortic dilatation.
III. Absence of all evidence of mitral disease, connoting rheumatic infection.
IV. Exertional dyspnoea.
V. The history of paroxysmal dyspnoea, often nocturnal.
VI. The history of pain, particularly paroxysmal pain.
VII. The presence of a positive Wassermann reaction.

In addition to the above as of clinical significance may we include

VIII. Progressive failure.

The evidence to be derived from the clinical course of these cases and characterised as "progressive failure" is unfortunately too well appreciated to need comment. It is towards combating the slow and subtle progress of the infection that the combined efforts of the profession the world over have been so tremendously stimulated.

The economic aspect alone of this series of 100 cases is told at a glance by the figures shown in Table VI.

TABLE VI

Economic aspect

Number of patients	100
Average admissions per patient	1.5
Total duration of stay in hospital, in weeks	619
Average stay per patient, in weeks	6.19
Duration of stay, in days	4,333
Cost to hospital at $4.00 per day	$17,332
Loss in wages, 85 males (3570 days at $4.00)	$14,280

Results

Improved (temporary)	53
Unimproved	12
Died (in the hospital)	35
Necropsies	33

It should be said for our figures giving the results that the 53 discharged from the hospital improved were most of them lost sight of. The improvement was at best but temporary and their subsequent history, though unknown, may be inferred. Of the 12 who left unimproved and against advice the end-result needs no telling.

Treatment

Although the essential objective of all treatment is the same in any and every patient, directed primarily against the infection and secondarily towards the relief of the late effects of the disease, the individuals concerned fall naturally into two great groups, the ambulatory and those admitted to the hospital. The observations outlined in this

brief résumé had to do solely with this latter group, always, unfortunately, constituting the less favorable cases because of the advanced vascular or myocardial lesions.

In no other condition that we encounter is the necessity of early recognition of the infection and the earliest possible institution of treatment of as great, or of any greater, importance than it is in cardio-vascular syphilis. It is evident that the greatest promise of successful treatment, with a reasonable prolongation of the expectancy of life, is met with in the ambulatory group in which the disease is recognised in its earliest stages. The seventh of our criteria for establishing a correct diagnosis tells the story, which is confirmed by everyone interested in this problem.

The method of treatment in vogue at the present time in our wards is essentially as follows: Depending, of course, upon the degree of circulatory embarrassment and subjective distress the usual therapeutic procedures for the relief of the cardiac failure are carried out. A Wassermann test is a routine measure for every admission; not infrequently this is reported as negative owing to previous treatment which the individual may have received in the outpatient Syphilis Clinic. In such instances the Wassermann test is always repeated when the patient is transferred back to the Syphilis Clinic on discharge from the hospital.

Digitalis is given essentially following the method as outlined by Eggleston (8) and the special symptoms are treated as the indications may arise. It is a clinical impression based upon a large series of such cases that the effects of digitalis in cardio-vascular syphilis are less satisfactory or less certain than in other types of cardiac failure. Possibly it would be more correct to say that its effects were more uncertain, recognising of course the fact that we do not expect to see the dramatic results of its administration, as evidenced in the presence of auricular fibrillation. It may well be that this impression is based upon a racial difference, as so many of the cases followed have been on the colored wards. It is astonishing how refractory the colored race is to a number of our common drugs. Some of these patients will tolerate extremely large doses of digitalis, 0.4 to 0.6 gm. daily up to 4 to 5 gm. without the slightest evidence of any physiological effect. And again, quite the antithesis of this fact is occasionally encountered.

We have seen the abrupt onset of a complete auriculo-ventricular dissociation after 1.6 gm. without any premonitory signs or symptoms. The only instances in which we have seen conspicuous alternation of the pulse attributable to digitalis therapy have been in cardio-vascular syphilitics, though these cases were all in white individuals.

Breitman (2), in an admirable discussion of the subject, quotes an amusing German aphorism which states that

> "Wenn man nicht weiss wo, wann, warum,
> Dann gibt man Jodkalium;"

To this rule we are no exception and potassium iodide is given routinely after the acute symptoms have been relieved, up to 10 to 12 gm. a day. To this is added either mercury in some form or neo-arsphenamine in small doses at the beginning, 0.1 to 0.2 gm. or bismuth salicylate, 2 cc. of a 10 per cent solution in olive oil, intramuscularly, 0.2 gm., the arsphenamine and the bismuth being given preferably alternately in courses of 4 to 6 weeks. It is understood of course that in the use of the arsenicals in these cases there is a certain element of danger involved in any but the most cautious procedure. We are making use of a double-edged weapon of defence. There is a vast literature dealing with the subject and many differences of opinion expressed as to the exact plan to be followed. It is a purely personal opinion that the danger lies not so much in the use of the arsenical in these cases even with advanced disease as in the failure to begin with the smallest dose and to proceed with caution. The danger of inducing a severe reaction analogous to the Herxheimer phenomenon has been frequently emphasised. Among the many paradoxes in medicine, and they are legion, nothing is more distressing than to achieve an arrest of the infection and yet to encounter a rapidly progressive advance of the cardiac failure and death "as a result of the dispersion of the syphilitic cardiac lesion." This has been called by Wile (35) a therapeutic paradox.

That we may, in some instances at least, lessen the symptoms of subjective distress and tide over an acute failure is admitted, but it is difficult indeed to elicit from any such series of cases as these cited evidence of lasting benefit; a mortality of 33 per cent in the wards, an improved 12 per cent, and, at best, but temporary aid to the remainder

of the series. By contrast and all the more promising, in that they represent the earlier ambulatory group, we are privileged, through the courtesy of Dr. Moore, to quote the results obtained in the out-patient Syphilis Clinic, as analysed by Dr. Danglade (5),[3] for a group of cases carefully studied and controlled. It should be clearly understood that these figures are no part of our series but represent the results obtained under the direction of Drs. Keidel and Moore in the Syphilis Clinic.

In order to avoid any question of inaccuracy of diagnosis the study was limited chiefly to patients with syphilitic aortic insufficiency and aneurysm. A group of such cases totalling 222 aortic insufficiencies and 93 with aneurysm was carefully sifted by Social Service visits, by consulting the in-patient records of six other hospitals in addition to those of the Johns Hopkins Hospital, and lastly by an examination of the death certificates of the city through the courtesy of the Baltimore City Health Department.

It was possible to trace the ultimate outcome of 90 individuals with aortic insufficiency and of 43 with aneurysm, to which eight additional cases comprising 3 undoubted instances of aortitis, 3 with syphilitic myocardial disease and 2 with angina pectoris have been added, a total of 141 cases.

The plan of treatment is as follows. First, all specific treatment is delayed until the signs of circulatory failure and the subjective symptoms of pain or paroxysmal dyspnoea with or without cardiac failure have been relieved by proper hospital care. Treatment is then begun with potassium iodide and bismuth or mercury. This is continued for at least 10 to 12 weeks. If at this time the patient has acquired an adequate cardiac reserve, the use of an arsenical preparation is cautiously begun. Neoarsphenamine or bismarsen (bismuth arsphenamine sulphonate given intramuscularly, 0.1 to 1.2 gm. dissolved in water). Bismuth salicylate, 2 cc. of a 10 per cent solution in olive oil, the equivalent of 0.2 gm., given intramuscularly, is also in very general use. The bismarsen may be acceptably used in those cases of cardio-vascular syphilis in which the intravenous use of the arsenical is contraindicated. The initial dose of neoarsphenamine is

[3] Presented before the meeting of the American Heart Association, June 24, 1930

usually 0.1 to 0.2 gm. at weekly intervals. This is continued for 10 to 12 weeks alternating with courses of bismuth and the iodides. This method of procedure is then continued for two years or more. The importance of avoiding any treatment reaction whatsoever is insisted upon. The following tables are based upon the results accomplished, depending upon the duration and thoroughness of the treatment and thus divide the cases studied into four groups, (1) those who had little adequate treatment; (2) those receiving the equivalent of one course

TABLE VII (*Dr. Danglade's Table I*)

The effect of treatment on the prolongation of life in aneurysm of the aorta

TREATMENT	TOTAL CASES	LIVING	DEAD	DURATION OF LIFE UNTIL DEATH OR LAST OBSERVATION, MEASURING FROM	
				Onset of symptoms	Start of treatment
				months	*months*
None or very little	11	0	11	9	6
Equivalent of one course of an arsenical or one long course of a heavy metal (1½–3 months)	12	8	4	34	28
Equivalent of one long course each of an arsenical and a heavy metal (3–12 months)	8	6	2	23	43*
More than one year of adequate treatment	12	7	5	69	55

* In this group there were 5 patients whose aortic aneurysms were discovered in the course of routine physical examination (confirmed in each case by roentgenographic and fluoroscopic examinations), the patients having suffered no symptoms referable to the aneurysm.

of an arsenical or one of a heavy metal 1½ to 3 months: (3) those receiving the equivalent of one long course each of an arsenical and bismuth 3 to 12 months; and (4) those who had more than one year of adequate care.

Two tables from Dr. Danglade's study are of great interest.[4] He has emphasised the fact "that the ultimate outcome is unfavorably influenced by the occurrence of cardiac failure before treatment is started, though even severe failure does not necessarily preclude a favorable result."

[4] Tables I and V of his series.

TABLE VIII (*Dr. Danglade's Table V*)

The average duration of life in treated patients with aortic insufficiency

TREATMENT GROUP	TOTAL CASES	PATIENTS LIVING	AVERAGE DURATION OF LIFE FROM		PATIENTS DEAD	AVERAGE DURATION OF LIFE FROM	
			Onset of symptoms	Beginning of treatment to present		Onset of symptoms to death	Beginning of treatment to death
			months	*months*		*months*	*months*
None or very little	25	5	52		20	22	21
Equivalent of one short course of an arsenical or one long course of a heavy metal (1½–3 months)	32	7	62	49	25	21	12
Equivalent of two arsenical courses plus a heavy metal (3–6 months)	10	5	48	45	5	20	16
Equivalent of 3 arsenical courses (6–12 months)	11	8	60	41	3	35	28
More than one year of adequate treatment	20	20	65	58			

Results such as these, as promising as they are surprising, are indeed a source of great encouragement and illustrate in a dramatic way what may be accomplished by prolonged and thorough care.

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ANGINA AGRANULOCYTICA AND ITS TREATMENT[1]

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Agranulocytosis in its original meaning and in its recent comprehensive sense has become a topic of increasing interest in contemporary medical and surgical practice. It has been my fortune and misfortune to see a relatively large number of patients suffering from a type of this disorder for which the term angina agranulocytica will be retained in this communication.

The first patient in whom I recognized the condition died in 1925. She was the mother of a noted literary critic, was 67 years old, had a sore throat with the characters of a follicular tonsillitis, developed the clinical picture of Ludwig's angina on the third day and was admitted to the Union Memorial Hospital in great respiratory distress, desperately ill. In the routine blood examination the medical house officer could find no leukocytes; in subsequent attempts he was able to report 700 with no polymorphonuclears. In the hope of relieving the respiratory embarrassment, on the fourth day of the illness Dr. Finney incised the cervical swelling with its overlying dusky red, tender, hot, oedematous skin, but the process advanced rapidly to the other side of the neck and the patient was dead twenty-four hours later.

That was in 1925. Three years before, namely, in November 1922 Werner Schultz (1) first stimulated interest in certain peculiar throat disorders accompanied by a defect of the granulocytic system.

Because of the absence of polymorphonuclear and other granular elements in the blood of these patients, he proposed the name *agranulocytosis* to designate the condition—a name which is now a familiar medical term everywhere. Shortly thereafter Friedemann (2), being struck by the usual severe localization of the process in the throat, suggested the title *angina agranulocytotica*.

The first American report of the disorder was made by Beatrice Lovett (3) in November, 1924.

In 1927 I reported several cases at a meeting of the Society of

[1] Submitted for publication April 1, 1931.

Clinical Surgery. The report was published in the privately printed proceedings of that Society. At the time (1927) little interest was manifested in the disorder in this country. During the past four years, however, paper upon paper has been published, case upon case of many varieties of agranulocytosis has been reported, until confusion has become worse confounded. The confusion is in part unavoidable, because cases of an acknowledged syndrome will vary one from the other in unessential details. On the other hand, a state approaching nosologic chaos is created by the fact that the term agranulocytosis has been transferred from the original meaning, assigned to it by Werner Schultz, to a host of conditions characterized by leukopenia with diminution or absence of the granular hematologic elements, in which the etiologic agents are evident or in which one is dealing with examples of well recognized clinical entities. If Schultz' term *agranulocytosis* is to be applied, as it has been, to a group of disorders which includes arsenical and benzol poisonings, leukopenic states due to radiation, certain instances of aplastic anaemia, some cases of aleukaemic leukaemia, conditions associated with obvious bacterial infections and examples of many of the acute infectious diseases with low leukocyte counts and diminished percentages of polymorphonuclears—then, a modifying term must be prefixed to "agranulocytosis" in these cases, in order to differentiate them from the affection under present consideration. To this affection it seems desirable to apply Friedemann's term, slightly modified, and call it *angina agranulocytica*. It is a term well entrenched in medical nomenclature and is sufficiently descriptive of the clinical picture which the patient exhibits when applying for medical care.

That this condition is entitled to be regarded as a clinical entity will seem justified when it is recorded that in the last three cases of the disorder admitted to the Union Memorial Hospital, the Medical House Officers made the probable diagnosis of agranulocytic angina before the blood examinations had been made. They ventured the diagnosis in each case because a woman in middle age was suddenly taken ill with chilly sensations, an accompanying high temperature, general aching and a sore throat. The impression of the physician in attendance had been that the patient was suffering from influenza. She had become so ill and prostrated in a few hours or in a day or two

that the attending doctor doubted his diagnosis of grippe and had advised removal to the hospital. The hospital physicians were confronted by a woman wilted in appearance with pale skin, but with visible mucous membranes of good color. The usual signs of a febrile illness were present together with a sore throat characterized by ulceromembranous lesions on the tonsils. Similar lesions involved the oral mucosa. The gums were swollen, were abnormally red and bled easily. The expectation of discovering agranulocytosis was confirmed in each of these three cases by the leukocyte count of 200, 300 and 1900, respectively, with only one polymorphonuclear cell in each of the first two counts and 12 per cent in the third.

Of the fifteen cases of agranulocytic angina which form the basis of these remarks, fourteen were in women, eleven being forty years of age or over; all complained of sore throats and presented oropharyngeal lesions varying from the picture of follicular tonsillitis to necroses involving the fauces and oral mucosa. Three exhibited areas of cutaneous gangrene. Only one had jaundice, a sign upon which Werner Schultz originally laid much stress. The primary leukocyte count in this series averaged 900, though the individual estimates ranged from 0 to 2300; the average percentage of polymorphonuclear cells was 9 with a minimum figure of 0 and an initial maximum of 28.

From this group of fifteen patients, certain types of the disorder can be differentiated. There is the fulminating type, death ensuing in a few days. In a second class belong those whose illness is more prolonged and who either die or recover in a few weeks. These patients may present moderate cervical glandular enlargement or the brawny cervical induration of Ludwig's angina. A third division is represented by one of my patients who had three distinct attacks of angina agranulocytica, in January 1929, May, 1930 and November, 1930. In the last recurrence the leukocytes numbered 1800 with 28 per cent polymorphonuclears; two weeks later, when apparent recovery had taken place, the count was 4600 with 77 per cent of neutrophiles. More tragic was the fate of a nurse in the Johns Hopkins Hospital. She made an apparent recovery from this disorder in 1926 and almost exactly a year later suffered a relapse during which she died. This relapsing type is amply illustrated in the literature on the subject.

Finally, a fourth variety may be called sub-chronic and is exemplified by the only man in the series of fifteen patients. He was sick thirteen months; the necrotizing process caused a perforation of his hard palate, but he finally recovered from an illness during which his condition was frequently regarded as hopeless.

We have not encountered a chronic form of Schultz' syndrome. Perhaps the conception of agranulocytic angina should be enlarged so as to include a chronic type as illustrated by the unique case of recurrent agranulocytosis reported by Rutledge, Hansen and Thayer (4). In this patient, attacks of stomatitis associated with agranulocytosis, fever and constitutional symptoms had recurred at intervals of approximately three weeks throughout the life of a man twenty years of age.

The nature of agranulocytic angina is still in doubt. When medical care is sought, the patient is suffering from a severe infection localized either in the oropharynx or in some other mucous membrane, or the subject is laboring under the burden of a septicaemia. From the mouth and throat many organisms have been isolated and accused of a causal relation to the agranulocytosis. Vincent's organisms are most frequently encountered. A similar multiplicity of microörganisms has been demonstrated in the blood of some of the patients. However, the evidence suggests that all these organisms are secondary invaders.

From the blood of one of our patients, a woman of 62 years who died on the second day of her illness, pneumococci of type III were isolated. Her leukocyte count was 150 with no granular elements. At the necropsy the posterior part of her tongue and the adjacent pharyngeal mucosa were black in color, having undergone necrosis. The uterine mucosa had suffered a similar process.

Another patient, a woman 51 years old, had been treated for influenza for about a week before entering the hospital on February 12, 1931. She then had a temperature of 105°, an ulceromembranous sore throat, a necrotic lesion about 1 cm. in diameter in the vault of the hard palate, cervical glandular enlargement of the type of Ludwig's angina, leukocytes 200, polymorphonuclears 1 per cent. Repeated transfusions were given. However, the patient grew progressively worse; the skin over the cervical induration assumed a bluish black hue, a small area of gangrene developed in the nasal septum, the vulva became red and oedematous, signs of consolidation of both lower lobes of the lung developed and with increasing stupor and cyanosis the patient died four days after admission. The highest

leukocyte count was 700 with no neutrophiles. A nonhemolytic streptococcus was cultured from the blood.

At autopsy, the marrow of a rib appeared hypoplastic; a rare polymorphonuclear cell could be discovered. A section of the fibula showed complete aplasia of the marrow. The lower lobes of the lung were heavy. On section the appearance was that of an infarct. Microscopically, the alveoli were filled with a fibrinous, hemorrhagic material. There was no evidence of the presence of either polymorphonuclears or lymphocytes; an occasional large mononuclear cell was seen loaded with blood pigment. Throughout the sections there were masses of granular material stained by the hematoxylin; some alveoli were filled with these clumps. Under the oil-immersion lens these were found to be masses of cocci, some arranged in chain formation. From the heart's blood a non-hemolytic streptococcus was grown.

Our present hypothesis as to the sequence of events in agranulocytic angina is in accord with the view propounded by Friedemann, a view which has received suggestive support from the blood studies of Rutledge, Hansen and Thayer (4) and more recently from Roberts and Kracke's observations (5). It is that the primary disorder lies in a depressed function of the granulocytic mechanism of the bone marrow with consequent agranulocytic leukopenia. Thereupon develops the lack of defense against infection which we have many reasons to believe the polymorphonuclear leukocytes in part afford. The cause of the defect in the leukopoietic system is totally obscure. None of our patients had suffered from any obvious infection immediately before the development of the sore throat. Some of them had felt exhausted months before the onset, but no blood examinations had been made during this period. One of them had had a sacro-iliac manipulation performed for the relief of backache a few weeks before the fatal illness; one had undergone hysteromyomectomy two months previous to the agranulocytic angina, from which she had recovered. Another had suffered from a prolonged attack of cystitis complicated by an extensive burn within the antecedent year.

It is possible that, if the leukocyte count had been made, agranulocytosis might have been detected during this state of ill health preceding the onset of the acute phase of the disorder.

Once the agranulocytic state has been established local or general infection or both follow; the characteristic necrotic mucous membrane lesions appear, a blood stream infection may supervene and a high

mortality results. A fatal issue was recorded almost invariably in the early reports on agranulocytic angina, but with the lapse of time occasional recoveries came to be recorded. It seems remarkable that as many as seven of the fifteen patients in our series recovered.

At this time it is impossible to draw decisive conclusions as to the efficacy of the measures that have been used in treating individuals suffering from this clinical entity. In the first place spontaneous recovery is possible.

In the case of a woman 51 years old, whom I saw with Dr. Finney in November, 1926, a black gangrenous area about the size of a thumb-nail developed over the most prominent part of a left lateral cervical glandular swelling on the fifth day. The necrotic skin and underlying tissues sloughed, a serous fluid exuded and the patient recovered in the course of four weeks. In this case the lesion in the throat was that of an ulceromembranous pharyngitis. The lowest total white count was 1500, the lowest percentage of polymorphonuclear leukocytes was 2. Without any active treatment whatever the leukocytes at the end of the fourth week numbered 6000, polymorphonuclears 58 per cent. The patient had recovered and is still well almost five years later.

The natural power of recovery therefore complicates deductions made from the results following the use of any therapeutic agent. Furthermore, even making allowance for the *vis medicatrix naturae* the treatment in our series has been in the majority of instances polypragmatic.

Of the eight patients who died two had the fulminating type, the rest were either not treated by the methods now commonly employed or were treated late in the course of the disorder.

Of the seven who have apparently recovered no treatment was applied in the case of one. The other six were treated by repeated transfusions of citrated blood; one of these by transfusions and leukocytic extract and three by transfusions and radiation of the bones. These three also had vigorous local treatment applied to the necrotic oropharyngeal lesions. All received the usual care given to patients suffering from acute infections.

Illustrating the progress of the condition of a patient under the combined treatment of transfusions, radiation and local medication the following case history may be cited.

On June 21, 1930, a woman, 51 years old, complained of sore throat and aching all over.

During the previous winter and spring she had suffered from headache and felt weak and unduly fatigued. As a result of a physical examination in April, 1930, a uterine myoma was discovered. There had been a rather profuse menstrual flow at regular intervals during the preceding two months. The hemoglobin estimate on April 25, 1930 was 80 per cent, but a leukocyte count was not made. Hysteromyomectomy was performed May 12, 1930. The convalescence was uneventful.

On June 21st the date of onset of the sore throat the fauces appeared abnormally red, both tonsils were enlarged, a yellow exudate covered the left. The temperature was 101.4°. Streptococci were cultured from the throat. During the succeeding forty-eight hours the patient's condition became alarming; she seemed extremely prostrated and toxic; the lesion on the left tonsil had become necrotic in character, the adjacent posterior pillar and pharyngeal mucosa were similarly involved, the swollen tonsils and oedematous uvula almost filled the archway of the soft palate. The gums were swollen and red. Vincent's organisms were recovered from the oral lesion. The cervical glands were moderately enlarged and tender. The temperature rose to 103.4°. The leukocytes numbered 2,450 without granular elements; the red blood copuscles, 4,470,000, hemoglobin 88 per cent.

On June 23, the third day of illness, she was transfused with 440 cc. of citrated blood, but the following day no change in the hematologic picture was discernible. Thereafter, another transfusion of 500 cc. was given on June 24 and a third on June 29.

In the meanwhile radiation of the skeletal system was undertaken in the hope of stimulating the granulocytic mechanism of the bone marrow. The dates of the roentgenologic treatments were June 25, 26, 27 and July 1. No immediate effect on the leukocyte count was observed after any of these therapeutic efforts, and not until June 30, a week after the agranulocytosis had been detected, were polymorphonuclears seen in the blood smears. Another week had elapsed before definite improvement of the extremely ill patient ensued and coincidently 20 per cent of neutrophiles were discovered in the total count of 2,400 leukocytes. The mouth and throat lesions were treated by the local application of a solution of potassium chlorate and copper sulphate.

A thrombosis of the left popliteal vein on July 6 was an incident in the stormy course of a desperate illness, from which the patient had apparently recovered four weeks after the onset. At that time, July 17, the leukocytes numbered 7,500; the polymorphonuclears 70 per cent.

Repeated transfusions were used early in the history of agranulocytosis. In our cases from 250 to 500 cc. of citrated blood were injected every other day or at longer intervals as indicated by the condition of the patient and by the leukocyte count. This method of treating the agranulocytic state is essentially empiric. No definite

conclusion as to its efficacy can be drawn from our experience or from the literature on the subject. Jagic and Spengler in their *Klinik und Therapie der Blutkrankheiten*, published in 1928, look upon "agranulocytosis as a particularly important indication for transfusion therapy" (6). On the other hand, other observers have recorded only failure after transfusions.

A second line of attack on this disorder which we have adopted follows the well known suggestion, made by Friedemann (7), in 1927, to apply in measured amounts of 1/20 E.D. roentgen rays to the bones of the skeleton. Friedemann radiated the long bones in four cases, giving one to three treatments at intervals of from two to several days. All four patients recovered. Friedemann observed a few hours after the application of the rays to both legs, in one instance also to the arms, an improvement in the general condition of the patient and in the blood a crisis-like change characterized by the appearance of numerous immature marrow cells. Radiation of the skeleton was thus used and is now advocated in the hope of stimulating the defective granulocytic function of the bone marrow. The stimulating quality of such small doses as those employed has been doubted by many roentgenologists. We have had the good fortune of having the coöperation of Dr. Waters in the roentgenologic treatment of our three radiated patients who have apparently recovered. The details of the technique as well as a critique of the method will be furnished in a supplementary paper by Waters and Firor.

The literature on radiotherapy of agranulocytosis discloses a divergence of opinion as to its value somewhat similar to that concerning the efficacy of blood transfusions. Our own impression has agreed with that expressed by Aubertin and Levy (8) in the *Archives des Maladies du Coeur* of 1928: "The efficacy of radiotherapy does not appear doubtful but it would be well to wait for further observations to appreciate its true value and to fix the rules of its application." Perhaps these further observations have been furnished in part by Friedemann (9), who in 1930 reported 13 recoveries in 15 nonfulminating cases, uncomplicated by sepsis or pneumonia, treated exclusively by radiotherapy. Others have had less favorable results. At present we think the attempt should be made promptly to influence the agranulocytic leukopenia by the expert application of roentgen rays.

Another method of attempting to stimulate polymorphonuclear production was employed in one of our patients. In this case the injection of leukocytic extract was practised in addition to blood transfusions. A somewhat similar therapy has been advocated recently by Reznikoff (10) under the title of "Nucleotide Therapy of Agranulocytosis." It involves the intravenous injection of 0.5 gram of the nucleotide in 20 cc. of physiologic saline solution. The compounds were salts of guanine and adenine obtained from the Eastman Kodak Company. While the nucleotide treatment seems worthy of further trial, no precise conclusions can be drawn from Reznikoff's results because in the treatment of his patients, as in ours, more than one therapeutic agent were used in the case of each of the three patients who recovered. In other words, in addition to the nucleotides, blood was also transfused. Since these nucleotides are not generally available, Squibb's leukocytic extract may be used in daily intramuscular injections of 50 cc. divided into two doses. There are in the literature some reports of recovery following this plan of therapy.

Even less convincing than the possible favorable effects obtained by transfusions, roentgenologic treatment and nucleotide therapy, are the results of other measures which presumably stimulate the formation of leukocytes. These include injections of turpentine, milk and other substances and are recorded in reports scattered through the medical journals.

Finally, the local treatment of the oropharyngeal lesions should be vigorously prosecuted. We have followed the technique of Dr. Coriell of this city. After nourishment has been taken, the mouth and throat are sprayed with a saturated solution of potassium chlorate, a compressed air atomizer being used. Following the spraying, each ulcerated area and the gums are swabbed with a solution of copper sulphate, 10 grains to the ounce. The oral treatment was carried out as often as five times a day in one of our cases. As the condition of the mouth and throat improves the treatment is less frequently applied, but whether Vincent's organisms are discovered or not, it seems advisable to refer the recovered patient to a competent dentist for further care.

To sum up, agranulocytic angina, as discussed in this communication, is a disorder usually occurring in women in the latter half of

life, characterized as a rule by necrotic ulcerations of the fauces, of the buccal mucosa or at times of other mucous membranes, accompanied by a defect in the granulocytic system, manifested by a leukopenia with diminished percentage or entire absence of the granular elements of the blood. The agranulocytosis probably precedes the sore throat, a circumstance which suggests the more frequent cytologic examination of the bood in private practice in general, and particularly in cases of sore throat which are not true to type. The process is eventually an infective, febrile illness of varying clinical types with a high rate of mortality.

Agranulocytic angina should be treated as a life-threatening emergency by immediate and repeated blood transfusions, the cautious radiation of the skeleton by an expert roentgenotherapeutist and the vigorous treatment of local lesions. The phlegmonous cervical mass, when present, has sometimes been incised to relieve respiratory obstruction, but as a rule it seems wise to abstain from surgical intervention, since no localized abscess forms under the existing agranulocytic state.

Even with such a program of therapy as outlined one approaches the treatment of these patients with hope rather than assurance.

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ROENTGENOTHERAPY OF ANGINA AGRANULOCYTICA

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In the present number of the JOHNS HOPKINS HOSPITAL BULLETIN Dr. Hamburger has discussed the classification, clinical types and treatment of agranulocytic angina. In the realm of treatment he has properly indicated the skepticism with which roentgenotherapy of this condition has been received. As a matter of fact, a number of questions arise in the minds of many as to the efficacy of bone-marrow irradiation; some may regard it dubiously; others, indifferently, and a few, perhaps, with favor. It is not expected that this brief discussion will deal with these questions decisively, but it is hoped that it will help to clarify the situation.

A review of the literature reveals that Friedemann, in 1927, first reported the results of irradiation. At that time he called attention to the immediate improvement which he had noted in four cases thus treated. A year later he reported the cases of two additional patients who survived, as well as of four which resulted fatally, three of the latter dying within twenty-four hours following the first treatment, the fourth developing a pneumonia with septicaemia. Since that time there have been reports of varying success both here and abroad. For the most part, however, it appears that these patients also received transfusions, treatment of throat lesions, and general stimulating therapy, so that one cannot be certain as to the part played by the roentgen-ray. More recently Friedemann has reported a series of forty-three treated exclusively by roentgen-irradiation with the exception of a few isolated cases in which a few ineffectual injections of Yatren-Kasein were given. Twenty-three of these patients died from complicating sepsis and five within 36 hours after irradiation; Friedemann does not feel that these should be considered in the evaluation of roentgen therapy. Of the remaining 15 uncomplicated cases, 13 were reported as cured. Improvement in the blood-picture in those surviving was usually noted within 24 to 36 hours after irradiation.

The original selection of 1/20th of an erythema dose was both fortuitous and, we might say, fortunate. Proceeding on the basis of the so-called Arndt-Schultz law that "small doses stimulate, large doses destroy," it was decided that a dosage which was likely to produce a biological effect without exceeding the stimulation limit was naturally the one to be used. Following the application of this dose in the first six cases Moldawsky found that in healthy adults there was also an increase in reticulocytes following such bone-marrow irradiation. Thoma later reported a not inconsiderable increase in the leucocytes in leukopenia resulting from typhoid when 1/20th of an erythema dose was used. One cannot be sure whether this apparent stimulation is the result of chemical changes in the blood or due to the ray itself. This question, therefore, must remain *sub judice;* certainly there is no evidence that a cell *per se* is affected by the roentgen-ray other than in a destructive manner. So far as we have been able to determine, those who have adopted this method of treating angina agranulocytica have all used 1/20th of an erythema dose. Voltage factors have ranged from 130,000 to 200,000; filtrations of 3 mm. aluminum, 6 mm. aluminum, 1 mm. aluminum plus 0.5 mm. copper, and 0.6 mm. copper alone have been used. It is interesting to note that some of Friedemann's patients began to show marked improvement following a single treatment with the use of a 0.6 mm. copper filter, whereas aluminum filtration often required three treatments to produce a similar effect. The total quantity of radiation administered is usually divided into three or four small doses.

The question as to the rationale of irradiation of the long bones has been asked several times. It is true that in the adult the marrow in the shafts of the long bones is mostly adipose tissue having little or no blood-forming function. Yet is is equally true that, when excessive or pathological demand exists, there is a formation of new centers by differentiation of the myeloblasts into granular myelocytes, the adipose tissue of the bone-marrow being replaced by this newly-formed tissue. It is possible that irradiation may aid in the formation of this new tissue. Furthermore, the cancellous portion of the long bones and some of the flat bones are included in the fields of radiation.

The first case treated by irradition in America was reported by Hodges in 1928 and resulted in recovery. With factors of 130,000

volts, 4 M. A., 6 mm. aluminum filter at 50 cm. the patient's lower extremities and throat were treated for two minutes at the first sitting, the upper extremities at the second. One minute was repeated over the femora.

Our personal experience has been limited to five patients. Four, treated between June and November of last year are still living. The fifth, almost in extremis when first seen, had to be treated in an institution where modern roentgen-therapeutic measures are not available and, unfortunately, died two days following the first treatment. Here, again, it is impossible to define the rôle played by the x-ray, as all these patients had other types of therapy. The lower extremities, the pelvis, upper humeri, and shoulder girdles were irradiated in the course of three or four treatments. Voltage values of 200,000 with aluminum and copper filtration, both separately and combined, with effective wave-lengths ranging from 0.197 Å units to 0.161 Å units, were used. The measurement of dosage was effected by the employment of a dosimeter reading in roentgen (R) units, adopting 600 units as the erythema dose, which was that agreed upon at the International Conference of Radiologists at Stockholm in 1928. It is obvious that where such a small dose is to be used an accurate determination is imperative.

In conclusion, the results of irradiation of the bone-marrow in angina agranulocytica, though not definitely ascertainable as yet, justify, in our opinion, a trial of such therapy whenever possible for these unfortunate patients.

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